(54) Title: PEPTIDE MIMETICS OF THE CYTOKINE RECEPTOR GAMMA CHAIN

(57) Abstract

Peptides which mimic a loop on the γ–chain that either interact with a cytokine or a γ–chain partner receptor chain of a heterodimeric cytokine receptor are disclosed. The peptides consist of 5–25 amino acids and inhibit signal transduction mediated by cytokine:receptor binding of cytokines that bind to receptors that comprise a γ–chain. Pharmaceutical compositions that comprise the peptides are disclosed. Methods of inhibiting signal transduction mediated by cytokine:receptor binding of cytokines that bind to receptors that comprise a γ–chain, methods of inhibiting cytokine mediated cell growth, proliferation, function or activity, methods of treating patients suffering from a disease disorder or condition characterized by cytokine mediated cell growth, proliferation, function or activity and methods of preventing a condition characterized by cytokine mediated cell growth, proliferation, function or activity are disclosed.

PEPTIDE MIMETICS OF THE CYTOKINE RECEPTOR GAMMA CHAIN

FIELD OF THE INVENTION

        The present invention relates to molecules which have
5   structures and functions that mimic the gamma chain that is
shared by several cytokine recpetors. The present invention
relates to the use of such molecules to modulate cytokine
activity and cytokine mediated functions.

BACKGROUND OF THE INVENTION

10   A family of related cytokine receptors including the
receptors for IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 have been
reported to share a common protein chain, the γ-chain, for
maximal ligand induced receptor binding and signaling. The γ-
chain is a member of the cytokine receptor superfamily which
15 includes receptors for growth hormone, erythropoietin, IL-3,
IL-2, IL-4, IL-7, IL-6 and GM-CSF. The γ-chain is a 64 kd
protein with a fibronectin type II and CKR-SF domain which
share structural homology.

        The crystal structure of the human growth hormone
20 receptor has been published by deVos A.M., et al. 1992 Science
255:306-312, which is incorporated herein by reference, and
shows that the receptors form a homodimer to bind ligand and
induce a signal. The receptors for IL-4 have been shown to be
in the form of a heterodimer consisting of IL-4α and the common
25 γ-chain. A model for the human IL-4:IL-4-Receptor interaction
has been published by Gustchina, A. et al. 1995 PROTEINS:

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Structure, Function and Genetics 21:140-148, which is incorporated herein by reference.

Cytokine:receptor complexes are very important mediators of many immune responses. For example, T cell growth
5 and differentiation is regulated in part by IL-2, IL-4, IL-7, IL-9, and IL-15. These cytokines have also been reported to play a role in other immunological functions as well.

Without the γ-chain, the cytokine receptors which normally form complexes with the γ-chain are much less
10 efficient in binding their ligands and thus transmitting their signals to the target cells. Evidence for the central role of the γ-chain includes the findings that mutations in this receptor have been demonstrated to be the causative factor in the development of severe combined immunodeficiency. Recently,
15 Boussiotis, V.A. *et al.* 1994 *Science* 266:1039-1047, which is incorporated herein by reference, demonstrated that the development of T cell anergy can be abrogated by signaling through this receptor by various means.

The function and activity of cells of the immune
20 system are regulated and directed by cytokine:receptor interactions as is signaling which induces growth and proliferation. The activation of T cells and B cells is regulated by cytokine:receptor interactions including cytokine:receptor interactions involving receptors which
25 include the γ-chain in a heterodimer.

There is a need for pharmaceutical compositions which can effectively inhibit the immune responses mediated by cytokine:receptor interactions. There is a need for a method of inhibiting cytokine mediated cell activation, function,
30 growth and/or proliferation. There is a need for pharmaceutical compositions which can effectively inhibit signaling that involves receptors which include the γ-chain. There is a need for compositions and methods which can inhibit or suppress immune responses in order to therapeutically or
35 prophylactically treat individuals who have conditions, diseases or disorders involving immune abnormal or undesirable immunological activity.

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SUMMARY OF THE INVENTION

The present invention relates to peptide mimics of the loops on the γ-chain which either interact with cytokines or the partners of the γ-chain in heterodimeric cytokine receptors that include the γ-chain. The peptides of the present invention are based on human and murine γ-chain sequences. The sequences homology for the human and murine γ-chain is high (71% identical and 82% similar) making the translation from one species to the next more direct.

The peptide mimics bind to the cytokine or partner receptor and inhibit cytokine activity. Inhibitors of the common γ-chain inhibit the function of IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 by preventing their binding to their respective receptors. Thus, the inhibition of these cytokine mediated events leads to immuno-suppressive responses which are beneficial for the prevention or treatment of numerous auto-immune diseases and graft rejection following various types of transplant procedures as well as diseases associated with hyperproliferation of T cells and/or B cells. For example, many lymphomas are dependent on some of these cytokines (IL-2 for T cell lymphomas and IL-4 for B cell lymphomas) for growth.

The present invention relates to peptides that consist of 5 to 25 amino acids including: SEQ ID NO:1 IQLYQTF, SEQ ID NO:2 IHLYQTF, SEQ ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID NO:5 CLQYLT, SEQ ID NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID NO:8 CLEHLTQ, SEQ ID NO:9 PIAGSSQQ, SEQ ID NO:36 PICGSSQQ, SEQ ID NO:10 PLCGSAQH, SEQ ID NO:11 PLAGSAQH, SEQ ID NO:12 NHEPRFLS, SEQ ID NO:13 DYRHKFSL, SEQ ID NO:14 LNLQNL, SEQ ID NO:15 LKLQNL, SEQ ID NO:16 NLSESQL, SEQ ID NO:17 KLSEQL or such an amino acid sequence with one or more conservative substitutions, wherein the peptide inhibits cytokine mediated signal transduction.

The peptides of the invention preferably have constrained conformations and most preferably are cyclic. In preferred embodiments, cysteine residues are provided at the

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termini of the peptides to form di-sulfide bonds which result in the formation of cyclic peptides.

According to some embodiments of the present invention, peptides are selected from the group consisting of:
5   SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19 CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID NO:24 CLQYLTQC, SEQ ID NO:25 CLEHLTQC, SEQ ID NO:26 CPIAGSSQQC, SEQ ID NO:37 CPICGSSQQC, SEQ ID NO:27 CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC,
10 SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC, SEQ ID NO:32 CLKLQNLC, SEQ ID NO:33 CNLSESQLC, SEQ ID NO:34 CKLSESQLC and derivative peptides thereof. The derivative peptides consist of amino acid sequences which contain one or more conservative substitutions.   Conservative substitutions include the
15 following:

          I may be substituted with V, A or L;
          Q may be substituted with N;
          L may be substituted with V, A or I;
          Y may be substituted with F;
20   V may be substituted with I, A or L;
          S may be substituted with T;
          A may be substituted with V, I or L;
          N may be substituted with Q;
          E may be substituted with D;
25   F may be substituted with Y;
          D may be substituted with E; and
          I may be substituted with V, A or L.

In some preferred embodiments, the V in sequences SEQ ID NO:3 CLQYLV and SEQ ID NO:4 CLEHLV are substituted with T
30 to improve solubility in aqueous solutions.   Accordingly, peptides SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID NO:24 CLQYLTQC and SEQ ID NO:25 CLEHLTQC are provided.

The peptides of the invention are derived from sequences of the murine or human cytokine receptor common gamma
35 chain.

The peptides correspond to murine cytokine receptor gamma common chain residues SEQ ID NO:1 IQLYQTF (100-106), SEQ

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ID NO:3 CLQYLV (161-166), PICGSSQQ (207-214), SEQ ID NO:12
NHEPRFLS (181-188), SEQ ID NO:14 LNLQNL (124-129), SEQ ID NO:16
NLSESQL (142-148) and the corresponding sequences from the
human cytokine receptor gamma common chain, i.e. SEQ ID NO: 2
5 IHLYQTF, SEQ ID NO:4 CLEHLV, SEQ ID NO:11 PLAGSAQH, SEQ ID
NO:13 DYRHKFSL, SEQ ID NO:15 LKLQNL and SEQ ID NO:17 KLSEQL.

The peptides SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19
CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID
NO:26 CPIAGSSQQC, SEQ ID NO:37 CPICGSSQQC, SEQ ID NO:27
10 CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC,
SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC and SEQ ID NO:32
CLKLQNLC are modeled to mimic the regions of the cytokine
receptor gamma common chain predicted to interact with ligands
and the peptides SEQ ID NO:33 CNLSESQLC and SEQ ID NO:34
15 CKLSESQLC are modeled to mimic the regions of the cytokine
receptor gamma common chain predicted to interact with other
cytokine receptor chains with which the gamma chain forms
heterodimers as an active receptor complex.

According to the invention, the peptides of the
20 invention inhibit cytokine mediated signaling that involves
cytokine receptors which include the gamma chain. Cytokines
IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 each interact with
receptor complexes that include the gamma chain. Accordingly,
the peptides of the invention can be used to inhibit IL-2, IL-
25 4, IL-7, IL-9, IL-13 and IL-15 signaling. Through this
inhibition, the peptides of the invention are useful to
suppress immunological responses and functions. For example,
these cytokines are involved in immunological activity in which
cells are induced to grow, proliferate and/or release factors,
30 cytokines or other molecules including antibodies. The
peptides of the invention can be used to inhibit these
activities.

Inhibition of T cell and/or B cell proliferation is
useful in the treatment of many diseases and conditions
35 including, but not limited to, leukemia, lymphoma, graft versus
host disease and other transplant rejections, allergies, asthma

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and autoimmune and inflammatory diseases such as rheumatoid arthritis, lupus, multiple sclerosis and myasthenia gravis. The peptides of the invention can also inhibit the growth of B cells and T cells and/or inhibit T cells and B cells from
5 releasing substances. Thus, by inhibiting cell growth and/or proliferation and/or function of cells involved in the immune system, the peptides can be useful to suppress the immune system.

The present invention relates to methods of preventing
10 and treating diseases involving or mediated by cells of the immune system. According to some embodiments of the invention, patients are administered compounds of the invention in an amount sufficient to suppress immune function sufficiently to have a therapeutic effect on patients suffering from such
15 diseases involving undesirable function, activity, growth or proliferation of cells of the immune system. According to some embodiments of the invention, patients are administered compounds of the invention in an amount sufficient to suppress immune function sufficiently to have a preventive effect on
20 patients at risk of developing diseases; disorders or conditions involving undesirable function, activity, growth or proliferation of cells of the immune system.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-1D shows data from experiments described
25 in Example 1 testing peptides gamma-4 and gamma-5 of the invention as described in Example 1 to determine their effect on the response of cells to exogenous cytokine IL-2 or IL-4. The cell line used proliferates in the absence of peptide. The data shows that the addition of peptide inhibits cell
30 proliferation in response to addition of the IL-4 and that such inhibition is dose dependent.

Figure 2 shows data from experiments described in Example 1 testing peptides of the invention as described in Example 1 to determine their effect on the response of cells
35 to exogenous murine IL-4. The cell line used proliferates in the absence of peptide. The data shows that the addition of

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peptide inhibits cell proliferation in response to addition of
mIL-4 and that such inhibition is dose dependent.

Figure 3 shows data from experiments described in
Example 1 testing peptides of the invention as described in
5 Example 1 to determine their effect on the response of cells
to exogenous murine IL-2. The cell line used proliferates in
the absence of peptide.

Figure 4 shows data from experiments described in
Example 1 testing the ability of peptides of the invention as
10 described in Example 1 to inhibit mixed lymphocyte responses
(MLR assays as described in Example 2).

Figure 5 shows data from experiments described in
Example 1 testing the ability of peptides of the invention as
described in Example 1 to inhibit CH12.CX proliferation.

15   Figures 6A-6F shows data from experiments described
in Example 2 testing the ability of peptides of the invention
as described in Example 1 to inhibit cytokine mediated activity
of various cell lines.

Figure 7 shows data from experiments described in
20 Example 2 testing the ability of peptides of the invention as
described in Example 1 to inhibit human IL-4 mediated activity.

Figure 8 shows data from experiments described in
Example 2 testing the ability of peptides of the invention as
described in Example 1 to inhibit cytokine mediated activity
25 of cells *in vivo*.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to molecules that have
a molecular surface similar to a molecular surface of cytokine
30 receptor common gamma chain. The peptides of the invention
interact with molecules which ordinarily interact with the
gamma chain and result in signal transduction. Not wishing to
bound by any theory, it appears that the peptides of the
invention thereby inhibit signal transduction by inhibiting
35 cytokine:receptor binding either by binding to the cytokine or
by binding to a cytokine receptor chain which forms

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heterodimers with the gamma chain in order to form a functional receptor complex.

According to some embodiments of the present invention, the invention can be represented by the formula:

$$R_1 - R_2 - R_3 - R_4 - R_5$$

wherein:

R_1, R_2, R_3, R_4 and R_5 taken together are 5- 25 amino acids or less and

R_1 is a linking moiety, preferably cysteine or penicillamine;

R_2 is 0-10 amino acids, preferably 0 amino acids;

R_3 is SEQ ID NO:1 IQLYQTF, SEQ ID NO: 2 IHLYQTF, SEQ ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID NO:5 CLQYLT, SEQ ID NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID NO:8 CLEHLTQ, SEQ ID NO:9 PIAGSSQQ, SEQ ID NO:10 PLCGSAQH, SEQ ID NO:11 PLAGSAQH, SEQ ID NO:12 NHEPRFLS, SEQ ID NO:13 DYRHKFSL, SEQ ID NO:14 LNLQNL, SEQ ID NO:15 LKLQNL, SEQ ID NO:16 NLSESQL, SEQ ID NO:17 KLSEQL or such an amino acid sequence with one or more conservative substitutions;

R_4 is 0-10 amino acids, preferably 0 amino acids; and

R_5 is a linking moiety, preferably cysteine or penicillamine.

It is preferred that R_1 is cysteine or penicillamine. It is more preferred that R_1 is cysteine.

It is preferred that R_2 is 0 amino acids.

It is preferred that R_3 is SEQ ID NO:1 IQLYQTF, SEQ ID NO: 2 IHLYQTF, SEQ ID NO:3 CLQYLV, SEQ ID NO:4 CLEHLV, SEQ ID NO:5 CLQYLT, SEQ ID NO:6 CLEHLT, SEQ ID NO:7 CLQYLTQ, SEQ ID NO:8 CLEHLTQ, SEQ ID NO:9 PIAGSSQQ, SEQ ID NO:10 PLCGSAQH, SEQ ID NO:11 PLAGSAQH, SEQ ID NO:12 NHEPRFLS, SEQ ID NO:13 DYRHKFSL, SEQ ID NO:14 LNLQNL, SEQ ID NO:15 LKLQNL, SEQ ID NO:16 NLSESQL or SEQ ID NO:17 KLSEQL.

It is preferred that conservative substitutions include I, V, A and L are interchangeable, Q and N are interchangeable, Y and F are interchangeable, S and T are interchangeable and E and D are interchangeable.

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It is preferred that R_4 is 0-1 amino acids. It is preferred that R_4 is 0 amino acids.

It is preferred that R_5 is cysteine or penicillamine. It is more preferred that R_5 is cysteine.

In preferred embodiments, the compound is SEQ ID NO:18 CIQLYQTFC, SEQ ID NO:19 CIHLYQTFC, SEQ ID NO:20 CLQYLVC, SEQ ID NO:21 CLEHLVC, SEQ ID NO:22 CLQYLTC, SEQ ID NO:23 CLEHLTC, SEQ ID NO:24 CLQYLTQC, SEQ ID NO:25 CLEHLTQC, SEQ ID NO:26 CPIAGSSQQC, SEQ ID NO:27 CPLCGSAQHC, SEQ ID NO:28 CPLAGSAQHC, SEQ ID NO:29 CNHEPRFLSC, SEQ ID NO:30 CDYRHKFSLC, SEQ ID NO:31 CLNLQNLC, SEQ ID NO:32 CLKLQNLC, SEQ ID NO:33 CNLSESQLC or SEQ ID NO:34 CKLSESQLC.

The present invention provides synthetic peptides that are 5-25 amino acids and comprise amino acid sequences from human or murine cytokine receptor gamma common chain. Non-gamma chain amino acid sequences are provided in some embodiments. The peptides are conformationally restricted, and are generally cyclized. In some embodiments, non-gamma chain sequences are included for the purposes of conformational restriction. In embodiments that comprise both gamma chain and non-gamma chain sequences, at least 20-25% of the amino acid sequence of the peptides of the present invention are derived from he gamma chain. It is preferred that greater than about 20-25% of the amino acid sequence of the peptides of the present invention are derived from the gamma chain, more preferably 30-40% and more preferably greater than 50%. In some embodiments, the percentage of amino acid sequence of the peptides of the present invention derived from gamma chain is about 60% or about 75% or more.

The peptides of the present invention may be prepared by any of the following known techniques. Conveniently, the peptides may be prepared using the solid-phase synthetic technique initially described in Merrifield (1963) *J. Am. Chem. Soc.* 15:2149-2154. Other peptide synthesis techniques may be found, for example, in M. Bodanszky *et al.*, *Peptide Synthesis*, John Wiley & Sons, 2d Ed. (1976); Kent and Clark-Lewis in *Synthetic Peptides in Biology and Medicine*, p. 295-358, eds.

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Alitalo, K., Partanen, P. and Vakeri, A., Elsevier Science
Publishers, (Amsterdam, 1985); as well as other reference works
known to those skilled in the art.   A summary of peptide
synthesis techniques may be found in J. Stuart and J.D. Young,
5   *Solid Phase Peptide Synthelia*, Pierce Chemical Company,
Rockford, IL (1984).   The synthesis of peptides by solution
methods may also be used, as described in *The Proteins*, Vol.
II, 3d Ed., p. 105-237, Neurath, H. et al., Eds., Academic
Press, New York, NY (1976).   Appropriate protective groups for
10   use in such syntheses will be found in the above texts, as well
as in J.F.W. McOmie, *Protective Groups in Organic Chemistry*,
Plenum Press, New York, NY (1973).

In general, these synthetic methods involve the
sequential addition of one or more amino acid residues or
15   suitable protected amino acid residues to a growing peptide
chain.   Normally, either the amino or carboxyl group of the
first amino acid residue is protected by a suitable,
selectively-removable protecting group.   A different,
selectively removable protecting group is utilized for amino
20   acids containing a reactive side group, such as lysine.

Using a solid phase synthesis as an example, the
protected or derivatized amino acid is attached to an inert
solid support through its unprotected carboxyl or amino group.
The protecting group of the amino or carboxyl group is then
25   selectively removed and the next amino acid in the sequence
having the complementary (amino or carboxyl) group suitably
protected is admixed and reacted with the residue already
attached to the solid support.   The protecting group of the
amino or carboxyl group is then removed from this newly added
30   amino acid residue, and the next amino acid (suitably
protected) is then added, and so forth.   After all the desired
amino acids have been linked in the proper sequence, any
remaining terminal and side group protecting groups (and solid
support) are removed sequentially or concurrently, to provide
35   the final peptide.   The peptide of the invention are preferably
devoid of benzylated or methylbenzylated amino acids.   Such
protecting group moieties may be used in the course of

synthesis, but they are removed before the peptides are used. Additional reactions may be necessary, as described elsewhere, to form intramolecular linkages to restrain conformation.

The present peptides may also be prepared by recombinant DNA techniques, although such methods are not preferred because of the need for purification and subsequent chemical modifications to conformationally restrain the peptides.

In addition to peptides which comprise L amino acids, pharmaceutical compositions according to the present invention may comprise peptides made up of D amino acids. Because most enzymes involved in degradation recognize a tetrahedral alpha-carbon, the D-amino acids were utilized in order to avoid enzyme recognition and subsequent cleavage. Our computer studies indicate that the same folded presentation of the peptide is accomplished by reversing the amino acid sequence, employing D-amino acids. Thus, peptides comprised of D amino acids are less susceptible to degradation.

Conservative substitutions in the amino acid sequence may be made. Those having ordinary skill in the art can readily design compounds of the invention with conservative substitutions for CD8 amino acids. For example, following what are referred to as Dayhof's rules for amino acid substitution (Dayhof, M.D. (1978) *Nat. Biomed. Res. Found.*, Washington, D.C. Vol. 5, supp. 3), amino acid residues in a peptide sequence may be substituted with comparable amino acid residues. Such substitutions are well known and are based the upon charge and structural characteristics of each amino acid.

Synthesized peptides may be circularized in order to mimic the geometry of those portions as they occur in the gamma chain. Circularization may be facilitated by disulfide bridges between cysteine residues. Alternatively, the peptides may be circularized by means of covalent bonds, such as amide bonds, between amino acid residues of the peptide such as those at or near the amino and carboxy termini.

Peptides for use in pharmaceutical compositions of the present invention may be designed following the guidelines set

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out herein and using well known processes. Methods of
synthesizing peptides and circularizing them may be performed
routinely using standard techniques and readily available
starting materials.

5   The present invention relates to methods of
therapeutically or prophylactically treating an individual
suffering from or susceptible to a disease, condition or
disorder associated with T cell or B cell growth, proliferation
and/or secretion of biologically active material. The present
10 invention relates to methods of therapeutically or
prophylactically treating an individual suffering from or
susceptible to a disease, condition or disorder by suppressing
immunological responses through the inhibition of cytokine
mediated signal transduction.

15   Examples of diseases condition and disorders for which
the present invention may be employed include T cell and B cell
leukemias and lymphomas, inflammatory and autoimmune diseases,
allergies and conditions and rejections associated with
transplantation protocols.

20   Those having ordinary skill in the art can readily
identify individuals suspected of suffering from or being
susceptible to conditions, diseases and disorders which can be
effectively treated or prevented by inhibition of cytokine
mediated immune responses effected by the peptides of the
25 invention. Those with ordinary skill in the art could readily
identify individuals for whom administration of the compounds
of the invention would be beneficial to alleviate or prevent
immune responses. Treatment may be provided prophylactically
or in response to symptoms associated with undesirable immune
30 responses or activity of cells of the immune system.
Pharmaceutical compositions useful in the methods of the
present invention comprise the compounds described herein.

         The method of therapeutically or prophylactically
treating an individual comprises administering to such an
35 individual an effective amount of a peptide according to the
invention. A prophylactically effective amount is an amount
which is effective to prevent or decrease the immune response

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associated with disease condition or disorder to be prevented.
A therapeutically effective amount is an amount which is
effective to decrease or eliminate symptoms in an individual
suffering from such diseases, conditions and disorders.

5   rejection. Those having ordinary skill in the art can readily
and routinely determine the ranges of both prophylactically and
therapeutically effective amounts of the peptides of the
invention without undue experimentation.

The present invention provides pharmaceutical
10 compositions that comprise the peptides of the invention and
pharmaceutically acceptable carriers or diluents. The
pharmaceutical composition of the present invention may be
formulated by one having ordinary skill in the art. Suitable
pharmaceutical carriers are described in *Remington's*
15 *Pharmaceutical Sciences*, A. Osol, a standard reference text in
this field, which is incorporated herein by reference. In
carrying out methods of the present invention, conjugated
compounds of the present invention can be used alone or in
combination with other diagnostic, therapeutic or additional
20 agents. Such additional agents include excipients such as
coloring, stabilizing agents, osmotic agents and antibacterial
agents.

For parenteral administration, the peptides of the
invention can be, for example, formulated as a solution,
25 suspension, emulsion or lyophilized powder in association with
a pharmaceutically acceptable parenteral vehicle. Examples of
such vehicles are water, saline, Ringer's solution, dextrose
solution, and 5% human serum albumin. Liposomes and nonaqueous
vehicles such as fixed oils may also be used. The vehicle or
30 lyophilized powder may contain additives that maintain
isotonicity (e.g., sodium chloride, mannitol) and chemical
stability (e.g., buffers and preservatives). The formulation
is sterilized by commonly used techniques. For example, a
parenteral composition suitable for administration by injection
35 is prepared by dissolving 1.5% by weight of active ingredient
in 0.9% sodium chloride solution.

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The pharmaceutical compositions according to the present invention may be administered as a single dose or in multiple doses. The pharmaceutical compositions of the present invention may be administered either as individual therapeutic
5 agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. In some embodiments, compounds are administered 1-2 days prior to transplantation, preferably 4-12
10 hours. Compounds may be delivered during transplantation procedures. In some embodiments, compounds are administered for 2 weeks to 2 months after transplantation procedures.

The pharmaceutical compositions of the present invention may be administered by any means that enables the
15 active agent to reach the targeted cells. These methods include, but are not limited to, oral, topical, intradermal, subcutaneous, intravenous, intramuscular and intraparenteral modes of administration. The compounds may be administered singly or in combination with other compounds. The compounds
20 of the invention are preferably administered with a pharmaceutically acceptable carrier selected on the basis of the selected route of administration and standard pharmaceutical practice.

The dosage administered varies depending upon factors
25 such as: pharmacodynamic characteristics; its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment; and frequency of treatment. Usually, the dosage of peptide can be about 1 to 3000 milligrams per 50 kilograms of body weight;
30 preferably 10 to 1000 milligrams per 50 kilograms of body weight; more preferably 25 to 800 milligrams per 50 kilograms of body weight. Ordinarily 8 to 800 milligrams are administered to an individual per day in divided doses 1 to 6 times a day or in sustained release form is effective to obtain
35 desired results.

EXAMPLES

Example 1

Novel peptide mimics that were derived from the sequence of the cytokine receptor common gamma chain were designed for the purpose of inhibiting cytokine receptor signal
5 transduction.   Such peptides are capable of inhibiting the functions of many immune cells which are responsive to these cytokines and thus are useful in the treatment of various maladies such as leukemia, lymphoma, inflammatory diseases, autoimmune disease, transplant rejection, allergies and others.
10   Based on the structural data, 5 sequences (γ1-5) were identified that are predicted to interact with the ligands of the γ-chain and one sequence (γ6) that is predicted to interact with the heterodimeric partner receptors was synthesized.   The sequences are as follows:

	Murine	Human	% Identity
γ1 $(I_{100}->F_{106})$	SEQ ID NO:1 IQLYQTF	SEQ ID NO:2 IHLYQTF	86
γ2 $(C_{161}->V_{166})$	SEQ ID NO:3 CLQYLV	SEQ ID NO:4 CLEHLV	67
γ3 $(P_{207}->Q_{214})$	SEQ ID NO:36 PICGSSQQ	SEQ ID NO:10 PLCGSAQH	63
γ4 $(N_{181}->L_{188})$	SEQ ID NO:12 NHEPRFLS	SEQ ID NO:13 DYRHKFSL	50
γ5 $(L_{124}->L_{129})$	SEQ ID NO:14 LNLQNL	SEQ ID NO:15 LKLQNL	83
γ6 $(N_{142}->L_{148})$	SEQ ID NO:16 NLSESQL	SEQ ID NO:17 KLSEQL	86

Peptides have been synthesized based on these sequences and cyclized by the addition of cysteine residues at either end and disulfide bridging. We have tested the following murine peptides in vitro for their ability to inhibit cytokine driven proliferation
25 of cell lines such as CTLL (T-cell) and CH12.CX (B-cell) as well as in MLRs:

Peptide	Sequence
$\gamma1$ $(I_{100}->F_{106})$	SEQ ID NO:18 CIQLYQTFC
$\gamma2$ $(C_{161}->V_{166})$	SEQ ID NO:20 CLQYLVC
$\gamma3$ $(P_{207}->Q_{214})$	SEQ ID NO:26 CPIAGSSQQC
$\gamma4$ $(N_{181}->L_{188})$	SEQ ID NO:29 CNHEPRFLSC
$\gamma5$ $(L_{124}->L_{129})$	SEQ ID NO:31 CLNLQNLC
$\gamma6$ $(N_{142}->L_{148})$	SEQ ID NO:33 CNLSESQLC
$\gamma2$ lin.	SEQ ID NO:35 ERCLQYLVQY
$\gamma2T$ $(\gamma2$ V->T)	SEQ ID NO:22 CLQYLTC

The murine sequences have been tested in at least two of these proliferation assays. Figures 1A-1D, 2 and 3 show the ability of these peptides to inhibit IL-4 induced proliferation of CTLL's. Figure 4 shows the ability of these peptides to inhibit MLRs and Figure 5 shows the ability of these peptides to inhibit CH12.CX proliferation.

These data suggest that these peptides can in fact inhibit cytokine responses in vitro. These peptides do not appear to be toxic as the CTLL proliferation to IL-2 is not affected.

Example 2

Experiments were performed to test the effect of each of peptides gamma-1, gamma-2, gamma-3, gamma-4, gamma-5 and gamma-6 on different cell types using several different assays. The data from the experiments is shown in Figures 6A-6F. The assays were performed as follows:

CTLL Proliferation Assay: The murine IL-2- and IL-4- responsive CTLL cell line was used to assess the ability of the gamma chain peptides to inhibit the binding of these cytokines to their respective receptors. The cell line proliferates in responses to exogenously added cytokine and inhibition of this proliferation by the peptides would be a result of blocking the cytokines from interacting with their receptors. Briefly, 5000 CTLL cells are added to the wells of a 96 well microtitre plate. Either 10 U/ml r-mIL-2 or 1 ng/ml r-mIL-4 are added to

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these wells along with titred amounts of the indicated peptides. Cultures are incubated at 37°C for 24 hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are deemed the

5 positive response and well containing no peptide and no cytokine are deemed the background (bkg) proliferation. A percent response is calculated as follows: (CPM experimental-CPM bkg)/CPM positive response-CPM bkg). All data are expressed in this manner.

10   CT4S Proliferation Assay: The murine IL-4 responsive CT4S cell line was used to assess the ability of the gamma chain peptides to inhibit the binding of IL-4 to its receptor. The cell line proliferates in responses to exogenously added mIL-4 and inhibition of this proliferation by the peptides

15 would be a result of blocking the mIL-4 from interacting with their receptors. Briefly, 5000 CT4S cells are added to the wells of a 96 well microtitre plate. r-mIL-4 (50 pg/ml) is added to these wells along with titred amounts of the indicated peptides. Cultures are incubated at 37°C for 48 hours and

20 pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are deemed the positive response and wells containing no peptide and no cytokine are deemed the background (bkg) proliferation. A percent response is calculated as follows: (CPM experimental-

25 CPM bkg)/(CPM positive response-CPM bkg). All data are expressed in this manner.

          CH12 Proliferation Assay: The CH12 murine B cell lymphoma, like many lymphomas, is an IL-4 producing cell line that is also dependent on IL-4 for proliferation. No exogenous

30 IL-4 is added to the wells of these cultures. Briefly, 1500 cells are added to each well along with titred amounts of the indicated peptides. Cultures are incubated at 37°C for 48 hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are

35 deemed the positive response and there is no true background response. A percent response is calculated as follows: (CPM

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experimental)/(CPM positive response). All data are expressed in this manner.

Mixed Lymphocyte Assay: Allogeneic murine mixed lymphocyte response assays were performed to determine if the
5 gamma chain peptides were capable of inhibiting this response as well. Assays were performed as previously described. Briefly, responder lymph node cells were isolated from SJL mice and stimulator spleen cells were located from (B6xCBA) F_1 mice responder cells (2×10^5/well) were plated in 96 well plates
10 along with irradiated stimulator cells (4×10^5/well). Titred amounts of gamma chain peptides were added to the indicated wells. Cultures are incubated at 37°C for 3 days and pulsed with ^{3}H-TdR for the final 18 hours to indicate amount of proliferation. Wells containing no peptide and both stimulator
15 and responder cells are deemed the positive response and wells containing no peptide and no stimulator cells are deemed the background (bkg) proliferation. A percent response is calculated as follows: (CPM experimental-CPM bkg)/(CPM positive response-CPM bkg). All data are expressed in this manner.

20   In vitro testing using human cells and in vivo testing was performed as follows.

TF-1 Proliferation Assay: The TF-1 cell line is a human cell line that is responsive to several cytokine including human IL-4. Inhibition of IL-4 induced proliferation
25 of this cell indicates that these peptides are capable if inhibiting human IL-4. Briefly, TF-1 cells are rested (Cultured in the absence of cytokines) for 48 hours prior to the initiation of the assay. Cells are plated (20000/well) along with titred amounts of the indicated peptides and 1 ng/ml
30 r-hIL-4). Cultures are incubated at 37°C for 48 hours and pulsed with ^{3}H-TdR for the final 6 hours to indicate amount of proliferation. Wells containing no peptide are deemed the positive response and wells containing no peptide and no cytokine are deemed the background (bkg) proliferation. A
35 percent response is calculated as follows: (CPM experimental-CPM bkg)/(CPM positive response-CPM bkg). All data are expressed in this manner. The results are shown in Figure 7.

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Effect of Gamma Chain Peptides *In Vivo*: In order to evaluate the efficacy of these peptides *in vivo*, we challenged sub-lethally (500Rads) irradiated B10.A mice with 2×10^5 CH12 (B-cell Lymphoma) cells and tracked the lethal effects of this tumor challenge. Indicated groups of mice (4/group) received either no treatment, gamma 2T (0.5 mg i.p. on days 0,3,6), of gamma4 (0.5 mg i.p. on days 0,3,6). Data is represented as % survival. The data is shown on Figure 8.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
    (i) APPLICANT: Townsend, Robert M.
                    Korngold, Robert
   (ii) TITLE OF INVENTION: Peptide Mimics of the Cytokine Receptor Common
                                  Gamma Chain and Methods and Compositions for
                                  Making and Using the Same
  (iii) NUMBER OF SEQUENCES: 37
   (iv) CORRESPONDENCE ADDRESS:
        (A) ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & Norris LLP
        (B) STREET: One Liberty Place, 46th Floor
        (C) CITY: Philadelphia
        (D) STATE: Pennsylvania
        (E) COUNTRY: USA
        (F) ZIP: 19103
    (v) COMPUTER READABLE FORM:
        (A) MEDIUM TYPE: Floppy disk
        (B) COMPUTER: IBM PC compatible
        (C) OPERATING SYSTEM: Windows 3.11
        (D) SOFTWARE: Wordperfect for Windows 6.1
   (vi) CURRENT APPLICATION DATA:
        (A) APPLICATION NUMBER:
        (B) FILING DATE:
        (C) CLASSIFICATION:
  (vii) PRIOR APPLICATION DATA:
        (A) APPLICATION NUMBER: US 60/036,941
        (B) FILING DATE: 07-FEB-1997
 (viii) ATTORNEY/AGENT INFORMATION:
        (A) NAME: DeLuca, Mark
        (B) REGISTRATION NUMBER: 33,229
        (C) REFERENCE/DOCKET NUMBER: TJU-2291
   (ix) TELECOMMUNICATION INFORMATION:
        (A) TELEPHONE: 215-568-3100
        (B) TELEFAX: 215-568-3439

(2) INFORMATION FOR SEQ ID NO:1:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ile Gln Leu Tyr Gln Thr Phe
 1   5

(2) INFORMATION FOR SEQ ID NO:2:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ile His Leu Tyr Gln Thr Phe
 1   5

(2) INFORMATION FOR SEQ ID NO:3:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
   (ii) MOLECULE TYPE: peptide
   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

SUBSTITUTE SHEET (RULE 26)

Cys Gln Tyr Leu Val
 1   5

(2) INFORMATION FOR SEQ ID NO:4:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Cys Leu Glu His Leu Val
 1   5

(2) INFORMATION FOR SEQ ID NO:5:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Cys Leu Gln Tyr Leu Thr
 1   5

(2) INFORMATION FOR SEQ ID NO:6:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Cys Leu Glu His Leu Thr
 1   5

(2) INFORMATION FOR SEQ ID NO:7:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Cys Leu Gln Tyr Leu Thr Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:8:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Cys Leu Glu His Leu Thr Gln
 1   5

(2) INFORMATION FOR SEQ ID NO:9:
    (i) SEQUENCE CHARACTERISTICS:

```
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Pro Ile Ala Gly Ser Ser Gln Gln
  1               5


(2) INFORMATION FOR SEQ ID NO:10:
        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Pro Leu Cys Gly Ser Ala Gln His
  1               5


(2) INFORMATION FOR SEQ ID NO:11:
        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Pro Leu Ala Gly Ser Ala Gln His
  1               5


(2) INFORMATION FOR SEQ ID NO:12:
        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asn His Glu Pro Arg Phe Leu Ser
  1               5


(2) INFORMATION FOR SEQ ID NO:13:
        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide

        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asp Tyr Arg His Lys Phe Ser Leu
  1               5


(2) INFORMATION FOR SEQ ID NO:14:
        (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 6 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: both
        (ii) MOLECULE TYPE: peptide
        (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
```

Leu Asn Leu Gln Asn Leu
 1   5

(2) INFORMATION FOR SEQ ID NO:15:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 6 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Leu Lys Leu Gln Asn Leu
 1   5

(2) INFORMATION FOR SEQ ID NO:16:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asn Leu Ser Glu Ser Gln Leu
 1   5

(2) INFORMATION FOR SEQ ID NO:17:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 7 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: both
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Lys Leu Ser Glu Ser Gln Leu
 1   5

(2) INFORMATION FOR SEQ ID NO:18:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 9 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Cys Ile Gln Leu Tyr Gln Thr Phe Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:19:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 9 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Cys Ile His Leu Tyr Gln Thr Phe Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:20:
    (i) SEQUENCE CHARACTERISTICS:

                    (A) LENGTH: 7 amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Cys Leu Gln Tyr Leu Val Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:21:
        (i) SEQUENCE CHARACTERISTICS:
                    (A) LENGTH: 7 amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Cys Leu Glu His Leu Val Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:22:
        (i) SEQUENCE CHARACTERISTICS:
                    (A) LENGTH: 7 amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Leu Gln Tyr Leu Thr Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:23:
        (i) SEQUENCE CHARACTERISTICS:
                    (A) LENGTH: 7 amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Cys Leu Glu His Leu Thr Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:24:
        (i) SEQUENCE CHARACTERISTICS:
                    (A) LENGTH: amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Cys Leu Gln Tyr Leu Thr Gln Cys
 1   5

(2) INFORMATION FOR SEQ ID NO:25:
        (i) SEQUENCE CHARACTERISTICS:
                    (A) LENGTH: 8 amino acids
                    (B) TYPE: amino acid
                    (D) TOPOLOGY: circular
              (ii) MOLECULE TYPE: peptide
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Cys Leu Glu His Leu Thr Gln Cys

1   5

(2) INFORMATION FOR SEQ ID NO:26:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Pro Ile Ala Gly Ser Ser Gln Gln Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:27:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Cys Pro Leu Cys Gly Ser Ala Gln His Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:28:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Cys Pro Leu Ala Gly Ser Ala Gln His Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:29:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Cys Asn His Glu Pro Arg Phe Leu Ser Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:30:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 10 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: circular
    (ii) MOLECULE TYPE: peptide
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Cys Asp Tyr Arg His Lys Phe Ser Leu Cys
1   5   10

(2) INFORMATION FOR SEQ ID NO:31:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 8 amino acids
        (B) TYPE: amino acid

```
              (D) TOPOLOGY: circular
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Cys Leu Asn Leu Gln Asn Leu Cys
  1               5           10


(2) INFORMATION FOR SEQ ID NO:32:
        - (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: circular
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Cys Leu Lys Leu Gln Asn Leu Cys
  1               5           10


(2) INFORMATION FOR SEQ ID NO:33:
          (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 9 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: circular
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Cys Asn Leu Ser Glu Ser Gln Leu Cys
  1     '         5


(2) INFORMATION FOR SEQ ID NO:34:
          (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 9 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: circular
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Cys Lys Leu Ser Glu Ser Gln Leu Cys
  1               5


(2) INFORMATION FOR SEQ ID NO:35:
          (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 10 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: linear
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Glu Arg Cys Leu Gln Tyr Leu Val Gln Tyr
  1               5               10


(2) INFORMATION FOR SEQ ID NO:36:
          (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 8 amino acids
              (B) TYPE: amino acid
              (D) TOPOLOGY: linear
          (ii) MOLECULE TYPE: peptide
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Pro Ile Cys Gly Ser Ser Gln Gln
  1               5
```

(2) INFORMATION FOR SEQ ID NO:37:
        (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 10 amino acids
            (B) TYPE: amino acid
            (D) TOPOLOGY: linear
       (ii) MOLECULE TYPE: peptide
       (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Cys Pro Ile Cys Gly Ser Ser Gln Gln Cys
  1   5   10

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CLAIMS

1.   A peptide which mimics a loop on the γ-chain that either interact with a cytokine or a γ-chain partner receptor chain of a heterodimeric cytokine receptor, wherein said
5   peptide consists of 5-25 amino acids and inhibits signal transduction mediated by cytokine:receptor binding of cytokines that bind to receptors that comprise a γ-chain.

2.   The peptide of claim 1 wherein said peptide includes: SEQ ID NO:1 IQLYQTF; SEQ ID NO:2 IHLYQTF; SEQ ID NO:3 CLQYLV;
10   SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH; SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL; SEQ
15   ID NO:17 KLSEQL or such an amino acid sequence with one or more conservative substitutions.

3.   The peptide of claim 1 wherein said peptide includes: SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID NO:6 CLEHLT; SEQ
20   ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH; SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL or SEQ ID NO:17 KLSEQL.

25   4.   The peptide of claim 1 wherein said peptide includes: SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH; SEQ ID NO:11
30   PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL; SEQ ID NO:17 KLSEQL or such an amino acid sequence with one or more conservative substitutions.

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5.   The peptide of claim 1 wherein said peptide is conformationally restricted.

6.   The peptide of claim 1 wherein said peptide is cyclic.

7.   The peptide of claim 1 wherein said peptide has a
5   cysteine residue at its N terminus and a cysteine residue at its C terminus and it is cyclized by formation of a disulfide bond between said cysteine residues.

8.   The peptide of claim 1 wherein said peptide is selected from the group consisting of: SEQ ID NO:18 CIQLYQTFC;
10 SEQ ID NO:19 CIHLYQTFC; SEQ ID NO:20 CLQYLVC; SEQ ID NO:21 CLEHLVC; SEQ ID NO:22 CLQYLTC; SEQ ID NO:23 CLEHLTC; SEQ ID NO:24 CLQYLTQC; SEQ ID NO:25 CLEHLTQC; SEQ ID NO:26 CPIAGSSQQC; SEQ ID NO:37 CPICGSSQQC; SEQ ID NO:27 CPLCGSAQHC; SEQ ID NO:28 CPLAGSAQHC; SEQ ID NO:29 CNHEPRFLSC; SEQ ID NO:30 CDYRHKFSLC;
15 SEQ ID NO:31 CLNLQNLC; SEQ ID NO:32 CLKLQNLC; SEQ ID NO:33 CNLSESQLC; SEQ ID NO:34 CKLSESQLC and derivative peptides thereof.

9.   The peptide of claim 1 wherein said peptide is selected from the group consisting of: SEQ ID NO:18 CIQLYQTFC;
20 SEQ ID NO:19 CIHLYQTFC; SEQ ID NO:20 CLQYLVC; SEQ ID NO:21 CLEHLVC; SEQ ID NO:22 CLQYLTC; SEQ ID NO:23 CLEHLTC; SEQ ID NO:24 CLQYLTQC; SEQ ID NO:25 CLEHLTQC; SEQ ID NO:26 CPIAGSSQQC; SEQ ID NO:37 CPICGSSQQC; SEQ ID NO:27 CPLCGSAQHC; SEQ ID NO:28 CPLAGSAQHC; SEQ ID NO:29 CNHEPRFLSC; SEQ ID NO:30 CDYRHKFSLC;
25 SEQ ID NO:31 CLNLQNLC; SEQ ID NO:32 CLKLQNLC; SEQ ID NO:33 CNLSESQLC and SEQ ID NO:34 CKLSESQLC.

10.   The peptide of claim 1 wherein said peptide is a conformationally restricted peptide having the formula:
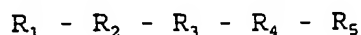
$$R_1 - R_2 - R_3 - R_4 - R_5$$

30 wherein:

R_1 is a linking moiety;

R_2 is 0-10 amino acids;

R$_3$ is SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH;

5   SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL; SEQ ID NO:17 KLSEQL or such an amino acid sequence with one or more conservative substitutions;

R$_4$ is 0-10 amino acids; and

10   R$_5$ is a linking moiety.

11.   The peptide of claim 10 wherein:
R$_1$ is cysteine; and
R$_5$ is cysteine.

12.   The peptide of claim 11 wherein:

15   R$_3$ is SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH; SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13

20   DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL; or SEQ ID NO:17 KLSEQL.

13.   The peptide of claim 12 wherein:
R$_1$ is cysteine; and
R$_5$ is cysteine.

25 14.   A pharmaceutical composition comprising a peptide of claim 1 and a pharmaceutically acceptable carrier or diluent.

15.   The pharmaceutical composition of claim 14 wherein said peptide includes: SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5

30   CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:10 PLCGSAQH; SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13 DYRHKFSL;

SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID NO:16 NLSESQL;
SEQ ID NO:17 KLSEQL or such an amino acid sequence with one or
more conservative substitutions.

16.   The pharmaceutical composition of claim 14 wherein
said peptide includes: SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2
IHLYQTF; SEQ ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5
CLQYLT; SEQ ID NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8
CLEHLTQ; SEQ ID NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID
NO:10 PLCGSAQH; SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS;
SEQ ID NO:13 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15
LKLQNL; SEQ ID NO:16 NLSESQL or SEQ ID NO:17 KLSEQL.

17.   The pharmaceutical composition of claim 14 wherein
said peptide is conformationally restricted.

18.   The pharmaceutical composition of claim 14 wherein
said peptide is cyclic.

19.   The pharmaceutical composition of claim 14 wherein
said peptide has a cysteine residue at its N terminus and a
cysteine residue at its C terminus and it is cyclized by
formation of a disulfide bond between said cysteine residues.

20.   The pharmaceutical composition of claim 14 wherein
said peptide is selected from the group consisting of: SEQ ID
NO:18 CIQLYQTFC; SEQ ID NO:19 CIHLYQTFC; SEQ ID NO:20 CLQYLVC;
SEQ ID NO:21 CLEHLVC; SEQ ID NO:22 CLQYLTC; SEQ ID NO:23
CLEHLTC; SEQ ID NO:24 CLQYLTQC; SEQ ID NO:25 CLEHLTQC; SEQ ID
NO:26 CPIAGSSQQC; SEQ ID NO:37 CPICGSSQQC; SEQ ID NO:27
CPLCGSAQHC; SEQ ID NO:28 CPLAGSAQHC; SEQ ID NO:29 CNHEPRFLSC;
SEQ ID NO:30 CDYRHKFSLC; SEQ ID NO:31 CLNLQNLC; SEQ ID NO:32
CLKLQNLC; SEQ ID NO:33 CNLSESQLC; SEQ ID NO:34 CKLSESQLC and
derivative peptides thereof.

21.   The pharmaceutical composition of claim 14 wherein
said peptide is selected from the group consisting of: SEQ ID

NO:18 CIQLYQTFC; SEQ ID NO:19 CIHLYQTFC; SEQ ID NO:20 CLQYLVC;
SEQ ID NO:21 CLEHLVC; SEQ ID NO:22 CLQYLTC; SEQ ID NO:23
CLEHLTC; SEQ ID NO:24 CLQYLTQC; SEQ ID NO:25 CLEHLTQC; SEQ ID
NO:26 CPIAGSSQQC; SEQ ID NO:37 CPICGSSQQC; SEQ ID NO:27
5 CPLCGSAQHC; SEQ ID NO:28 CPLAGSAQHC; SEQ ID NO:29 CNHEPRFLSC;
SEQ ID NO:30 CDYRHKFSLC; SEQ ID NO:31 CLNLQNLC; SEQ ID NO:32
CLKLQNLC; SEQ ID NO:33 CNLSESQLC and SEQ ID NO:34 CKLSESQLC.

22.   The pharmaceutical composition of claim 14 wherein
said peptide is a conformationally restricted peptide having
10 the formula:

$$R_1 - R_2 - R_3 - R_4 - R_5$$
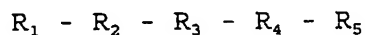
wherein:
        R_1 is a linking moiety;
        R_2 is 0-10 amino acids;
15   R_3 is SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ
ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID
NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID
NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH;
SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13
20 DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID
NO:16 NLSESQL; SEQ ID NO:17 KLSEQL or such an amino acid
sequence with one or more conservative substitutions;
        R_4 is 0-10 amino acids; and
        R_5 is a linking moiety.

25 23.   The pharmaceutical composition of claim 14 wherein:
        R_1 is cysteine; and
        R_5 is cysteine.

24.   The pharmaceutical composition of claim 23 wherein:
        R_3 is SEQ ID NO:1 IQLYQTF; SEQ ID NO: 2 IHLYQTF; SEQ
30 ID NO:3 CLQYLV; SEQ ID NO:4 CLEHLV; SEQ ID NO:5 CLQYLT; SEQ ID
NO:6 CLEHLT; SEQ ID NO:7 CLQYLTQ; SEQ ID NO:8 CLEHLTQ; SEQ ID
NO:9 PIAGSSQQ; SEQ ID NO:36 PICGSSQQ; SEQ ID NO:10 PLCGSAQH;
SEQ ID NO:11 PLAGSAQH; SEQ ID NO:12 NHEPRFLS; SEQ ID NO:13

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DYRHKFSL; SEQ ID NO:14 LNLQNL; SEQ ID NO:15 LKLQNL; SEQ ID
NO:16 NLSESQL; or SEQ ID NO:17 KLSEQL.

25.   The pharmaceutical composition of claim 24 wherein:
        R_1 is cysteine; and
5   R_5 is cysteine.

26.   A method of inhibiting signal transduction mediated
by cytokine:receptor binding of cytokines that bind to
receptors that comprise a γ-chain, said method comprising the
step of administering an effective amount of a peptide of claim
10 1.

27.   A method of inhibiting cytokine mediated cell growth,
proliferation, function or activity comprising the step of
contacting said cell with an peptide of claim 1.

28.   A method of treating a patient suffering from a
15 disease disorder or condition characterized by cytokine
mediated cell growth, proliferation, function or activity
comprising the step of administering to said patient a
therapeutically effective amount of a peptide of claim 1.

29.   A method of treating a patient suffering from a
20 disease disorder or condition characterized by cytokine
mediated cell growth, proliferation, function or activity
comprising the step of administering to said patient a
therapeutically effective amount of a peptide of claim 1,
wherein said patient has lymphoma, leukemia, an allergic
25 reaction, an autoimmune disease, graft versus host disease or
rejection of a transplant or graft.

30.   A method of preventing a condition characterized by
cytokine mediated cell growth, proliferation, function or
activity in a patient identified as being at risk of such a
30 condition comprising the step of administering to said patient
a prophylactically effective amount of a peptide of claim 1.

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31.   A method of preventing a condition characterized by cytokine mediated cell growth, proliferation, function or activity in a patient identified as being at risk of such a condition comprising the step of administering to said patient
5   a prophylactically effective amount of a peptide of claim 1, wherein said patient is at risk of an allergic reaction, graft versus host disease or rejection of a transplant or graft.
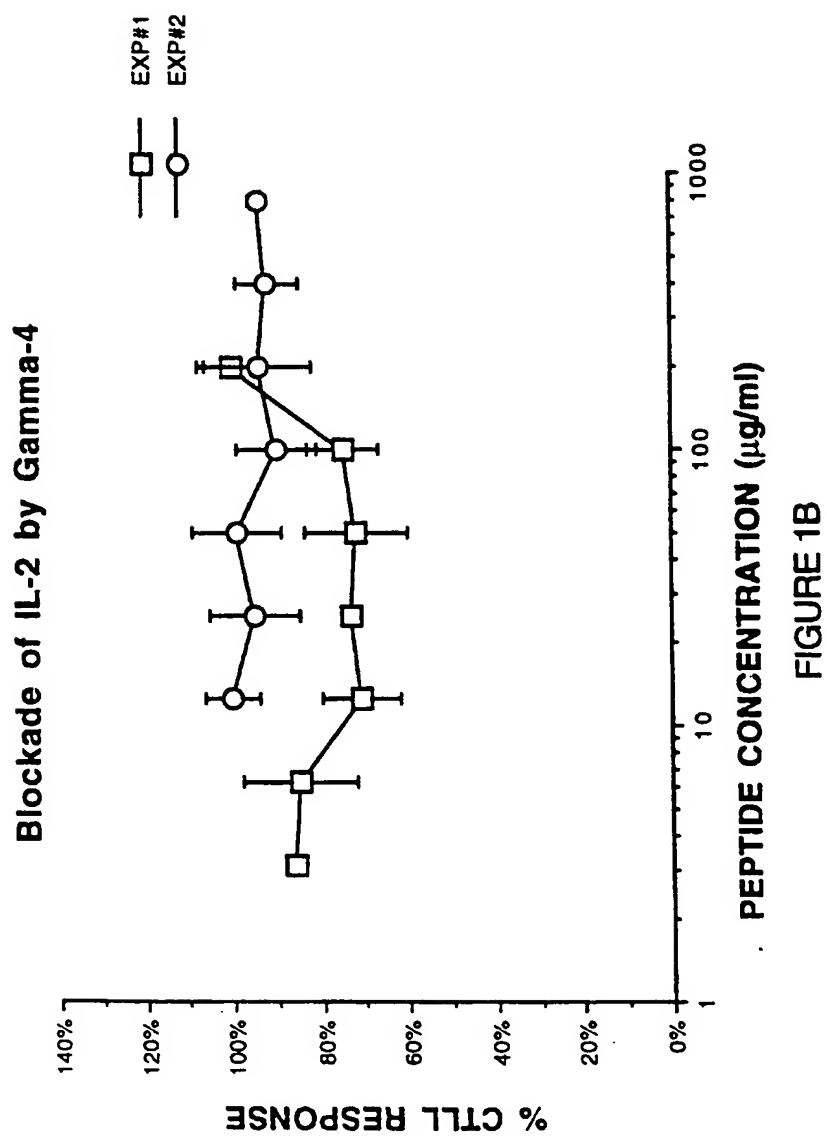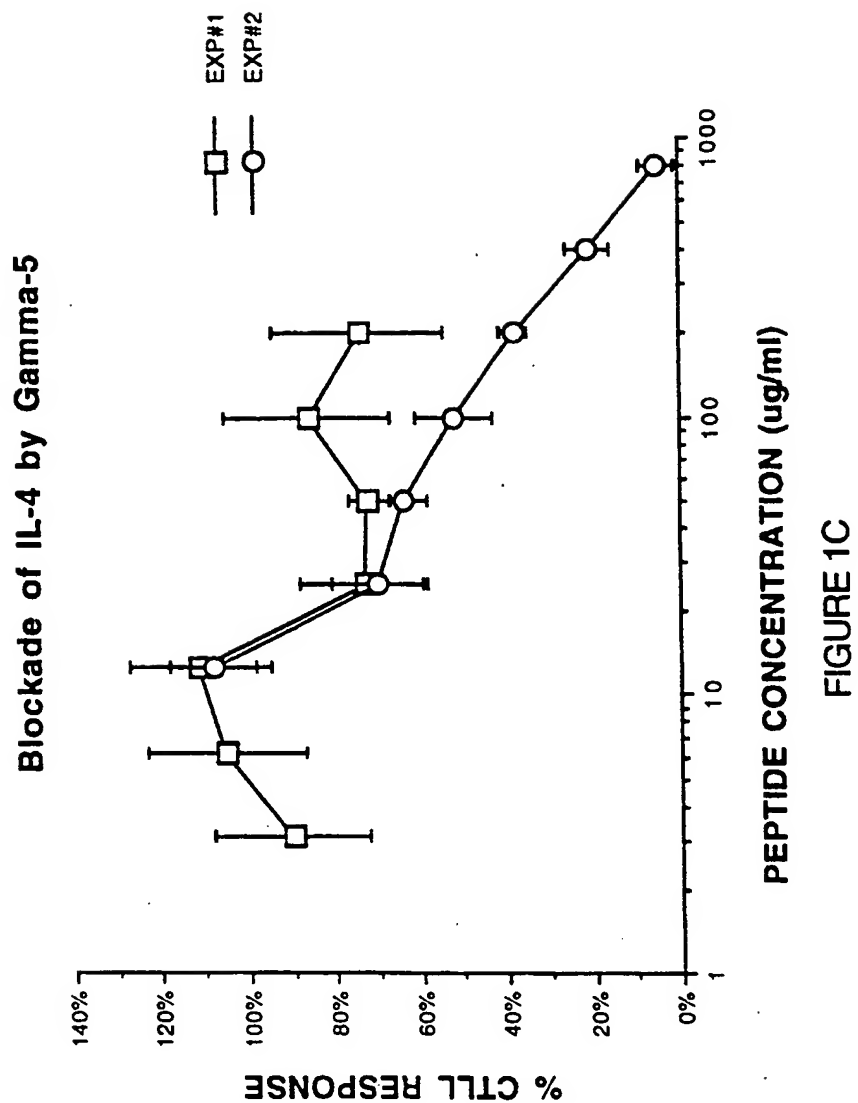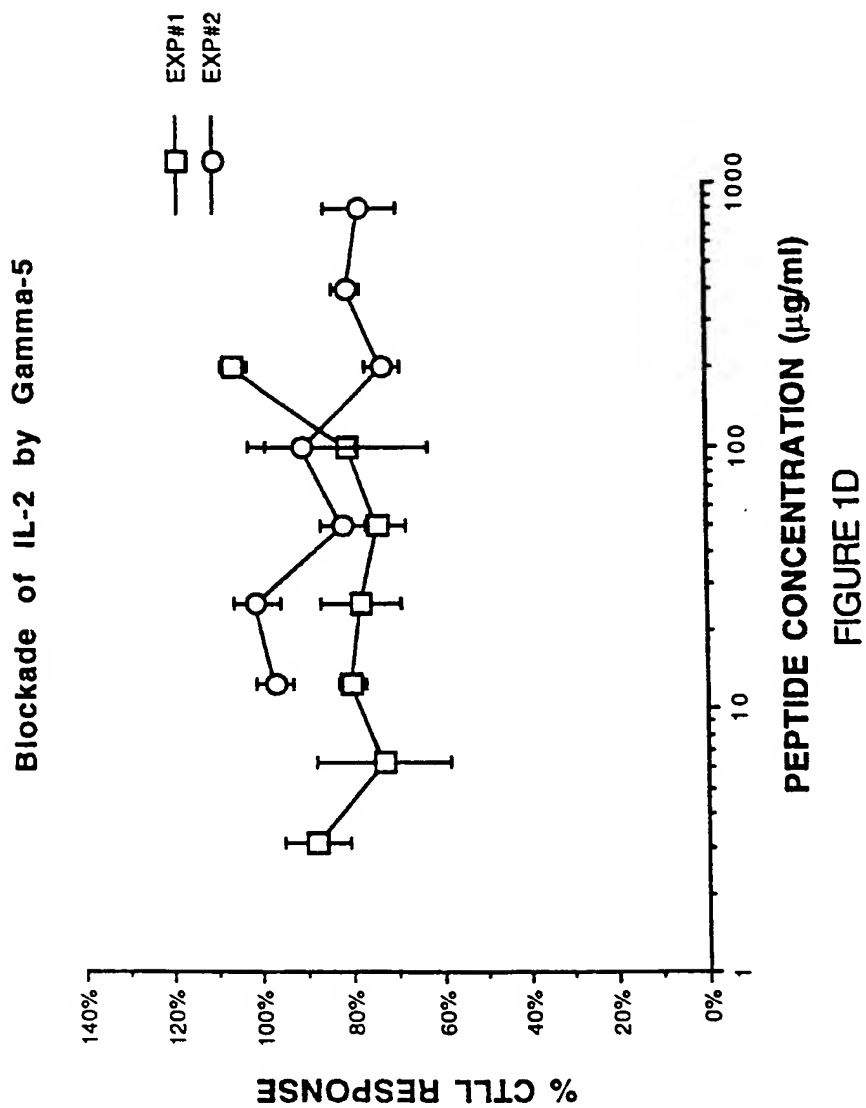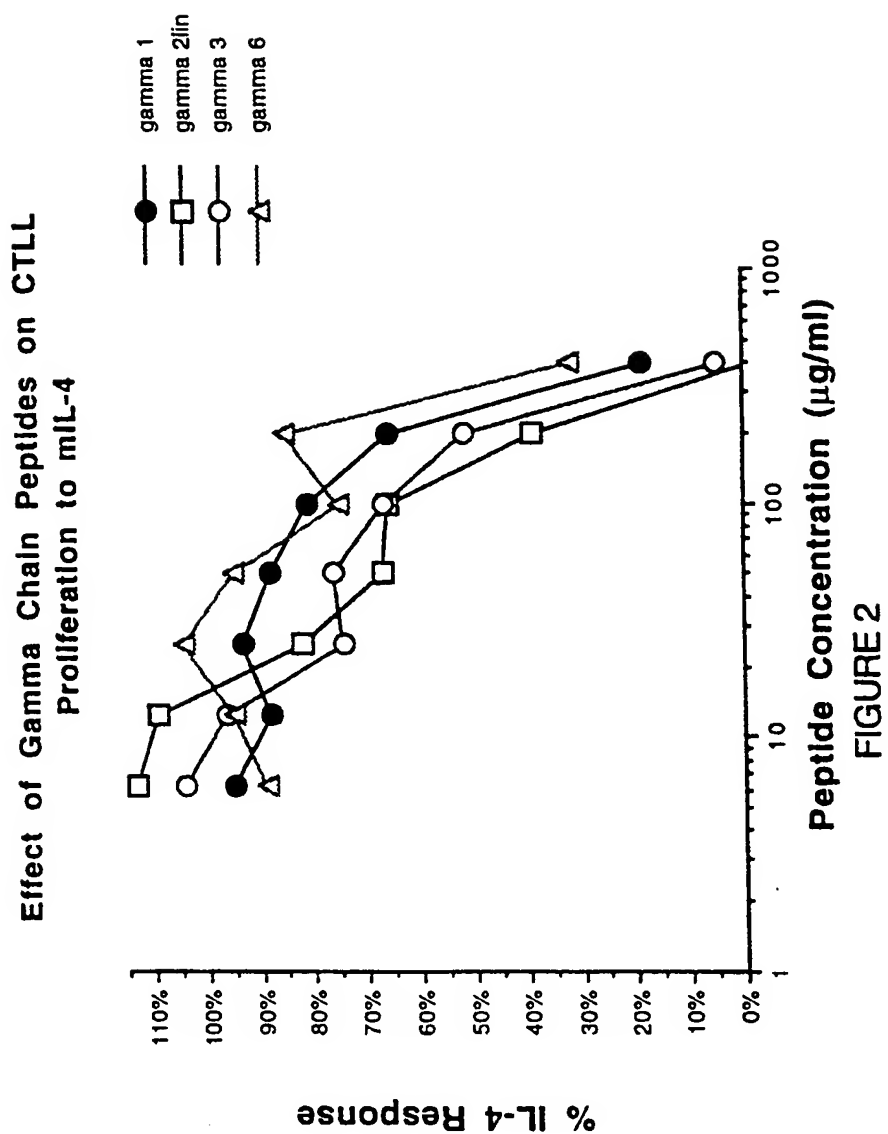
1/16
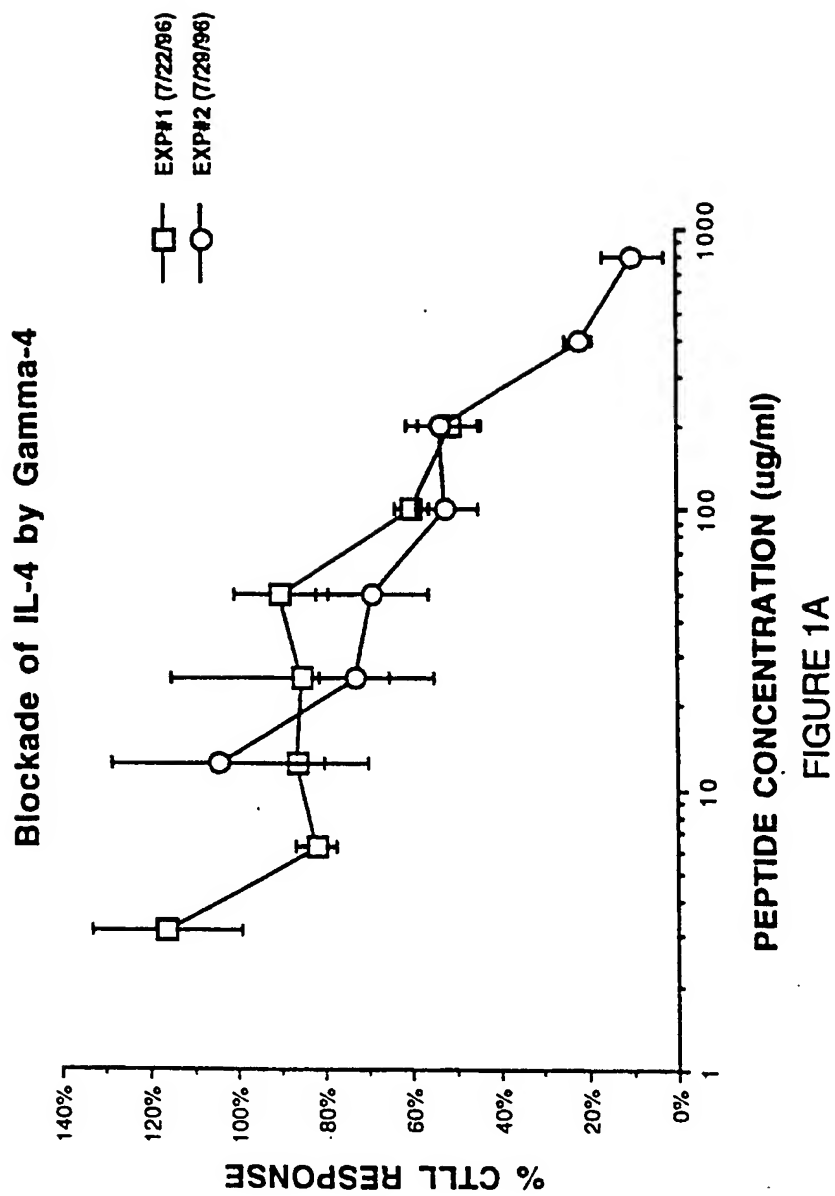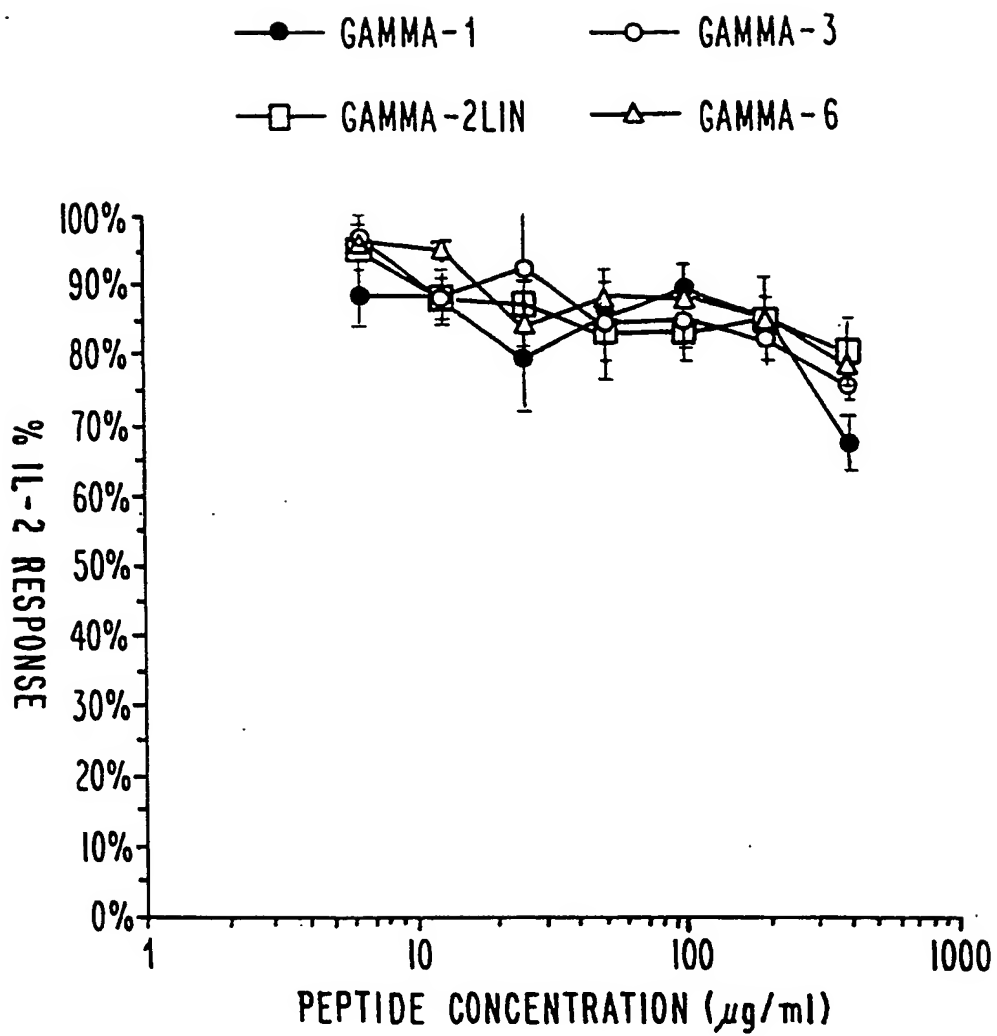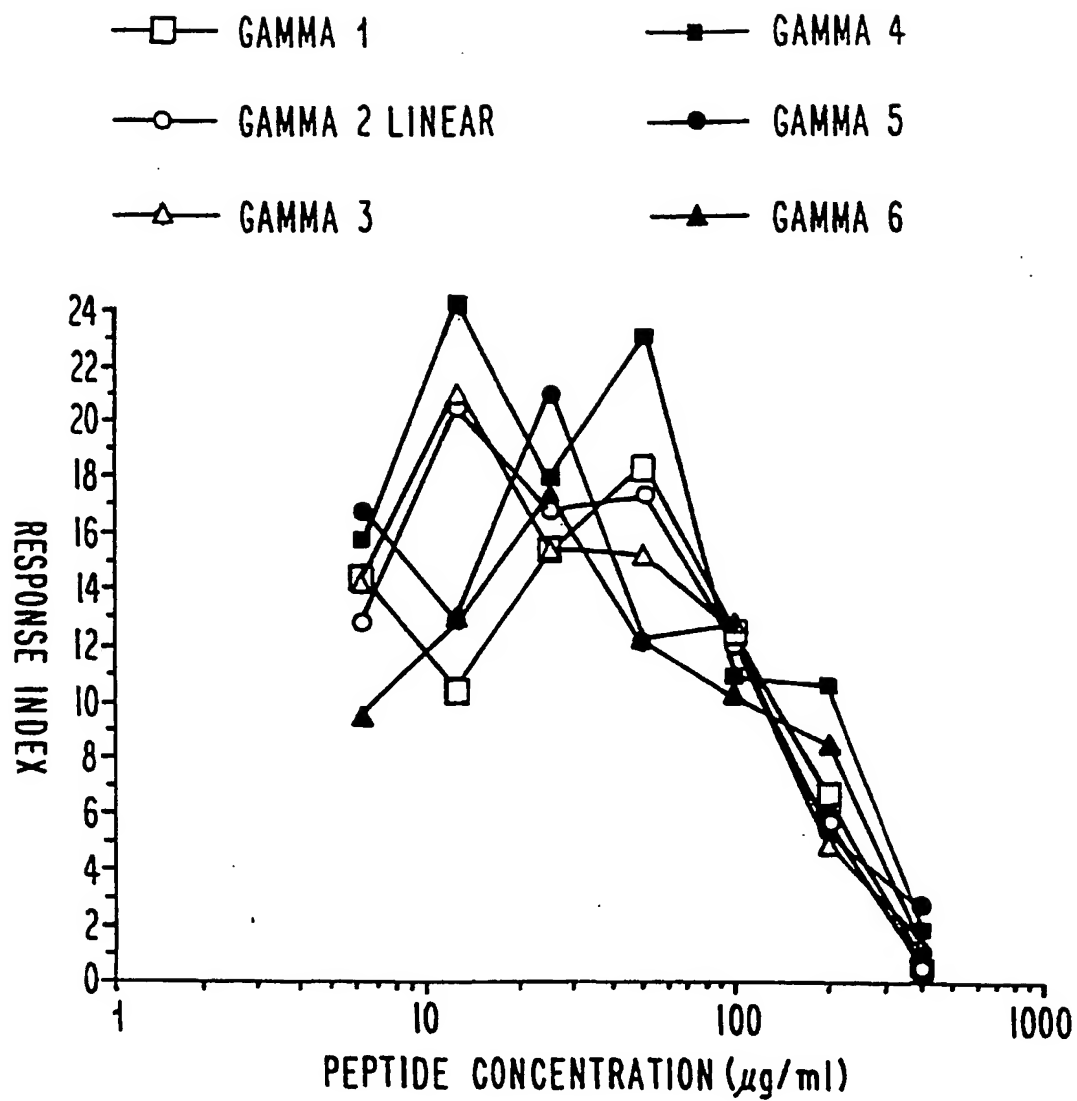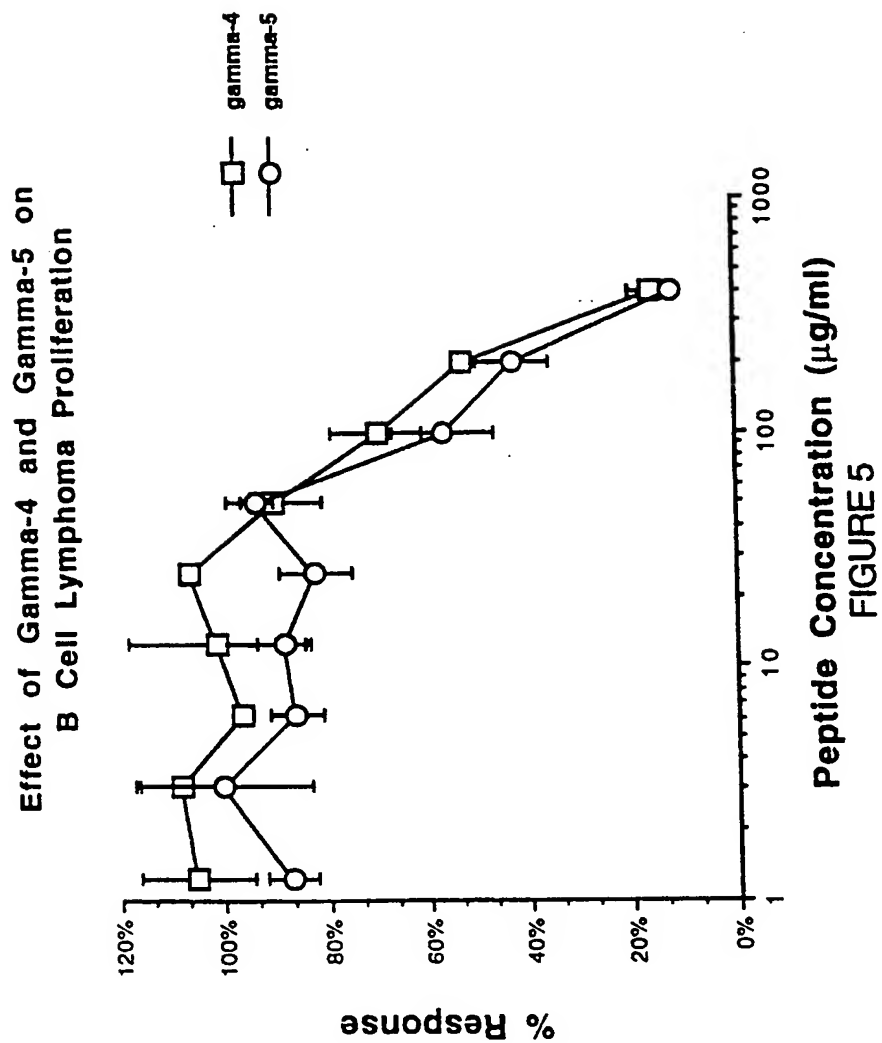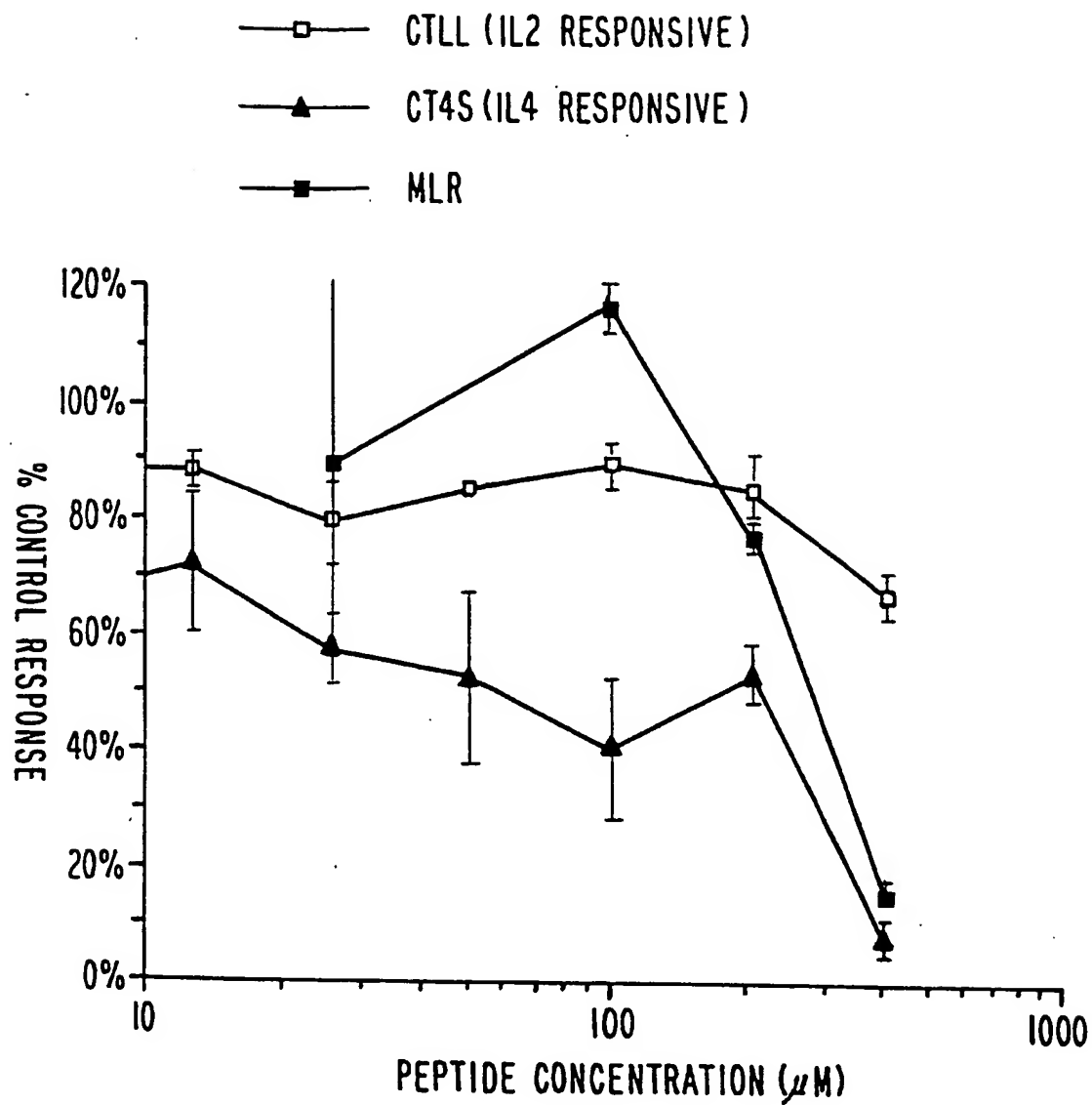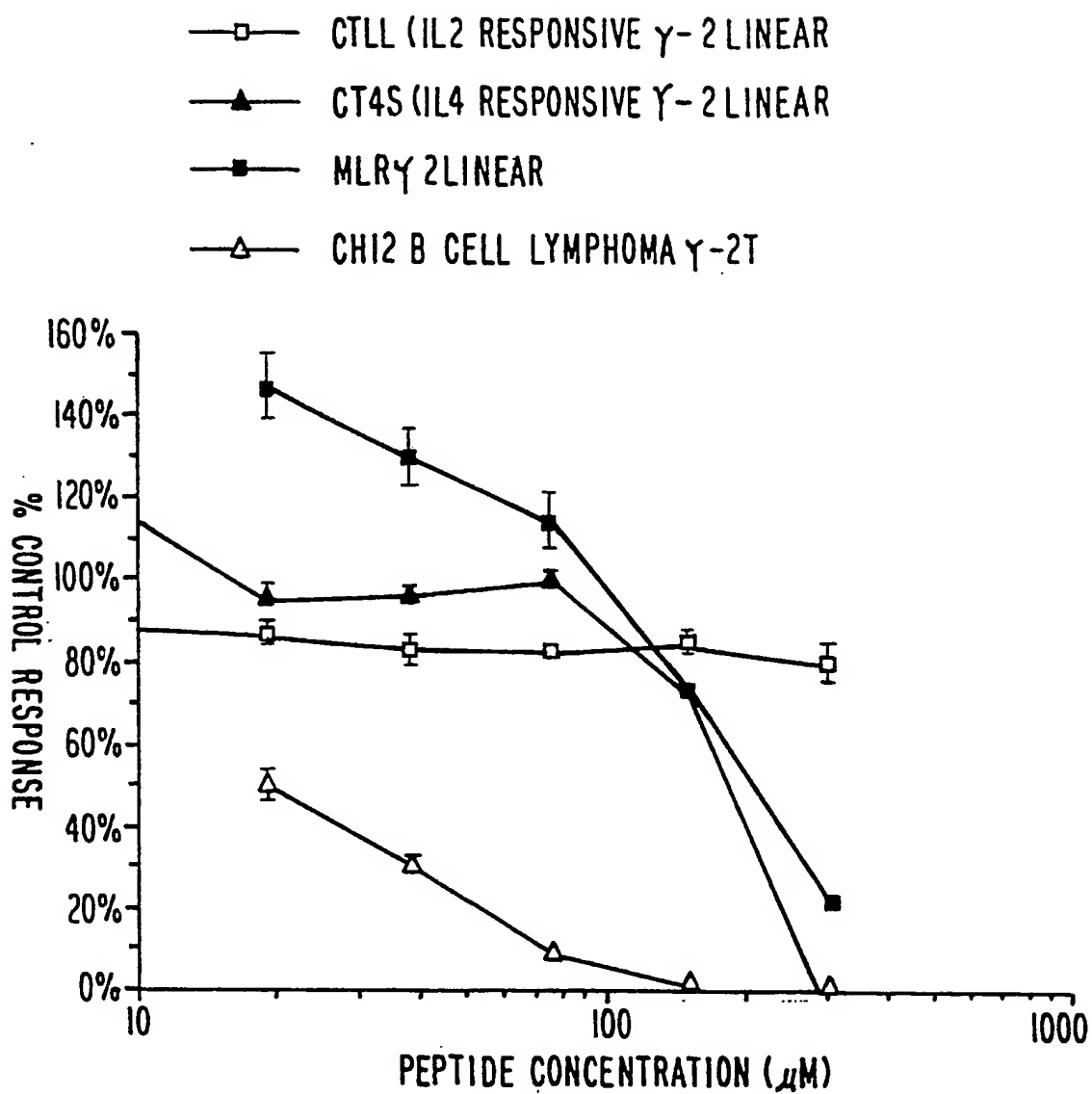
FIGURE 1A

Blockade of IL-2 by Gamma-4

FIGURE 1B

FIGURE 1C

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FIGURE 1D

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Effect of Gamma Chain Peptides on CTLL
Proliferation to mIL-4

FIGURE 2

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Fig. 3

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**Fig. 4**

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Effect of Gamma-4 and Gamma-5 on
B Cell Lymphoma Proliferation

Peptide Concentration (µg/ml)
FIGURE 5

% Response

gamma-4
gamma-5

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———□——— CTLL (IL2 RESPONSIVE)

———▲——— CT4S (IL4 RESPONSIVE)

———■——— MLR

Fig. 6A

—□— CTLL (IL2 RESPONSIVE γ-2 LINEAR

—▲— CT4S (IL4 RESPONSIVE γ-2 LINEAR

—■— MLR γ 2 LINEAR

—△— CH12 B CELL LYMPHOMA γ-2T

Fig. 6B

Fig. 6C

Fig. 6D

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- □ CTLL (IL2 RESPONSIVE)
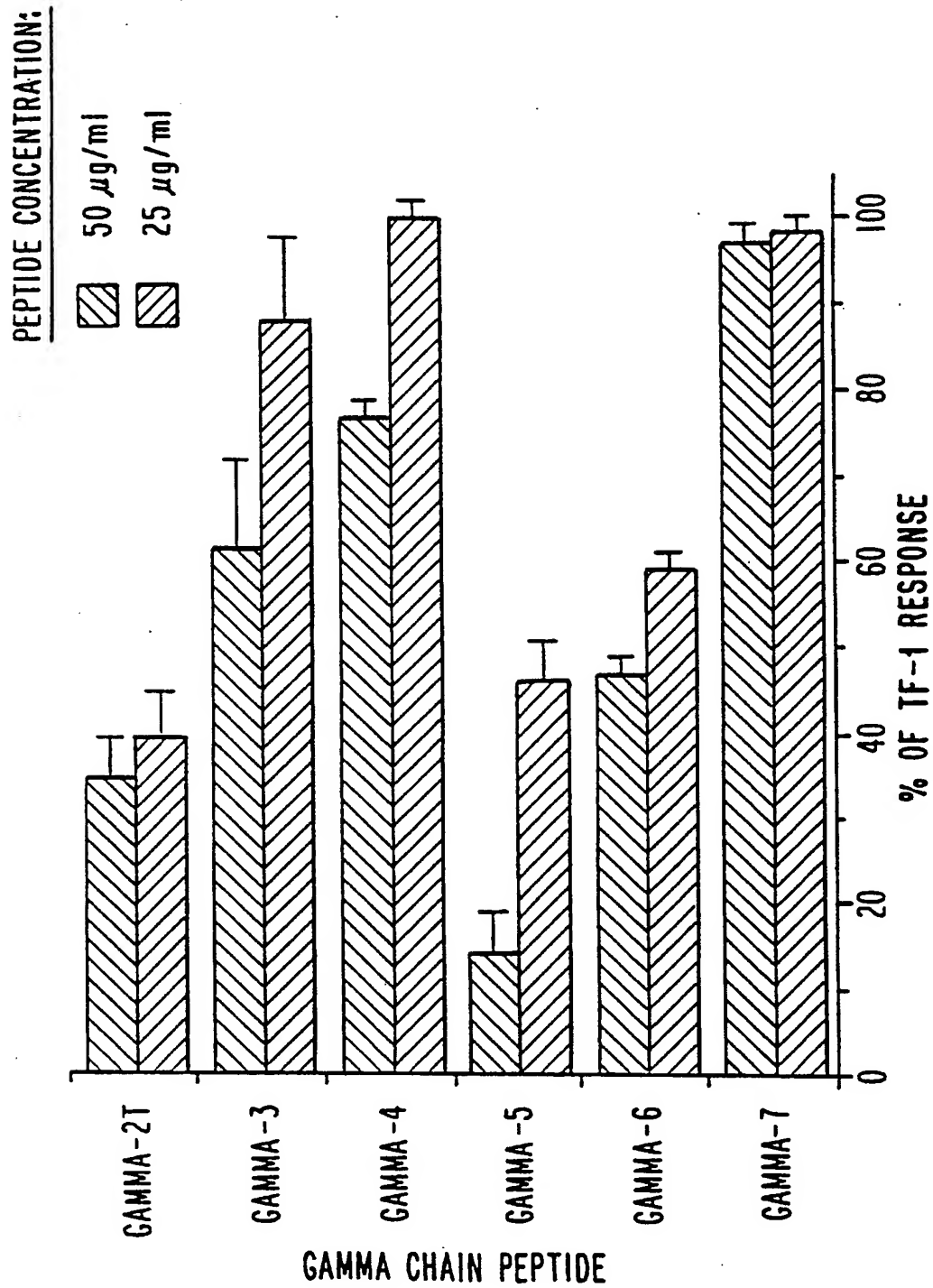- ▲ CT4S (IL4 RESPONSIVE)
- ■ MLR
- ● CHI2 B CELL LYMPHOMA
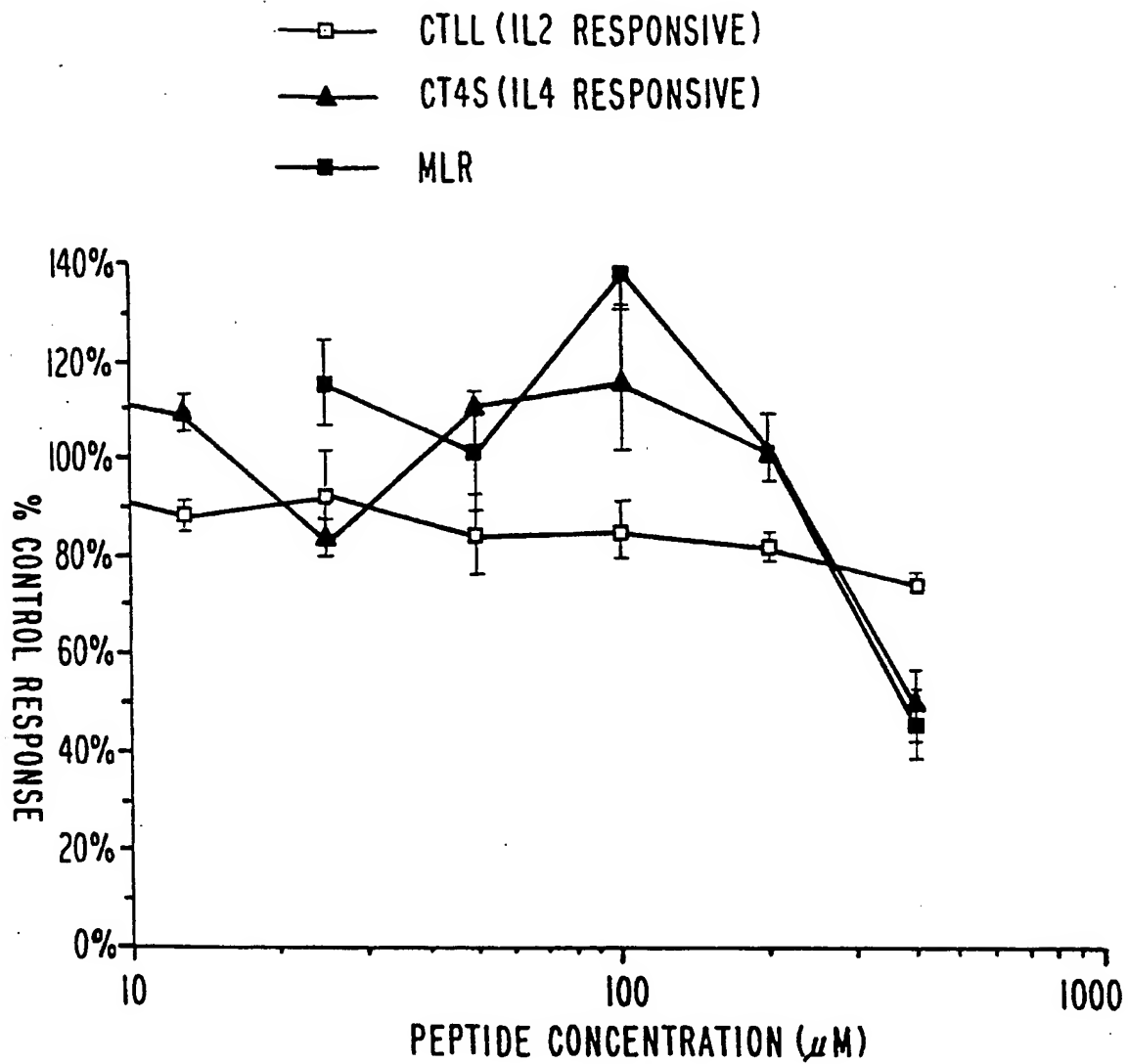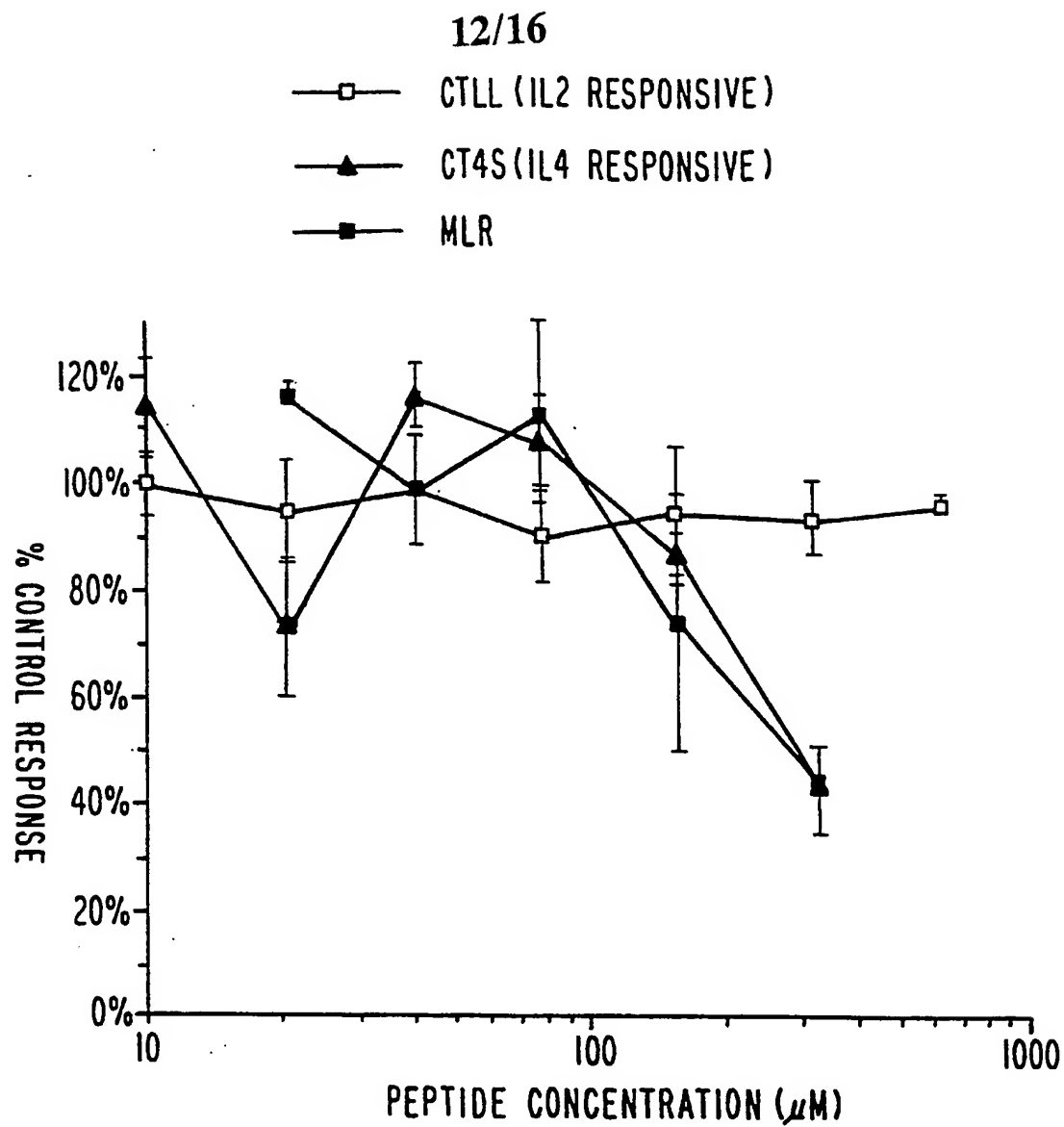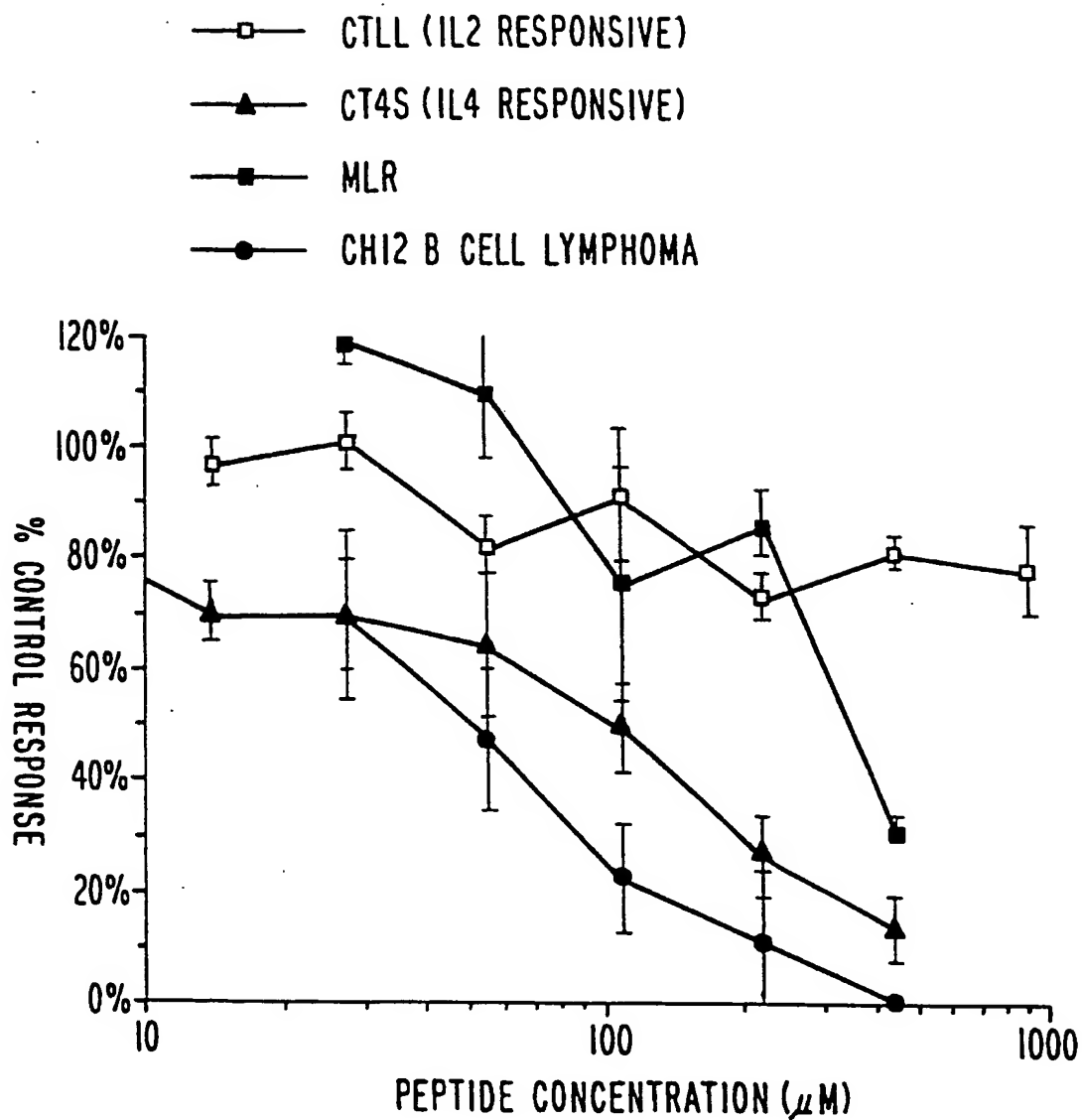
Fig. 6E

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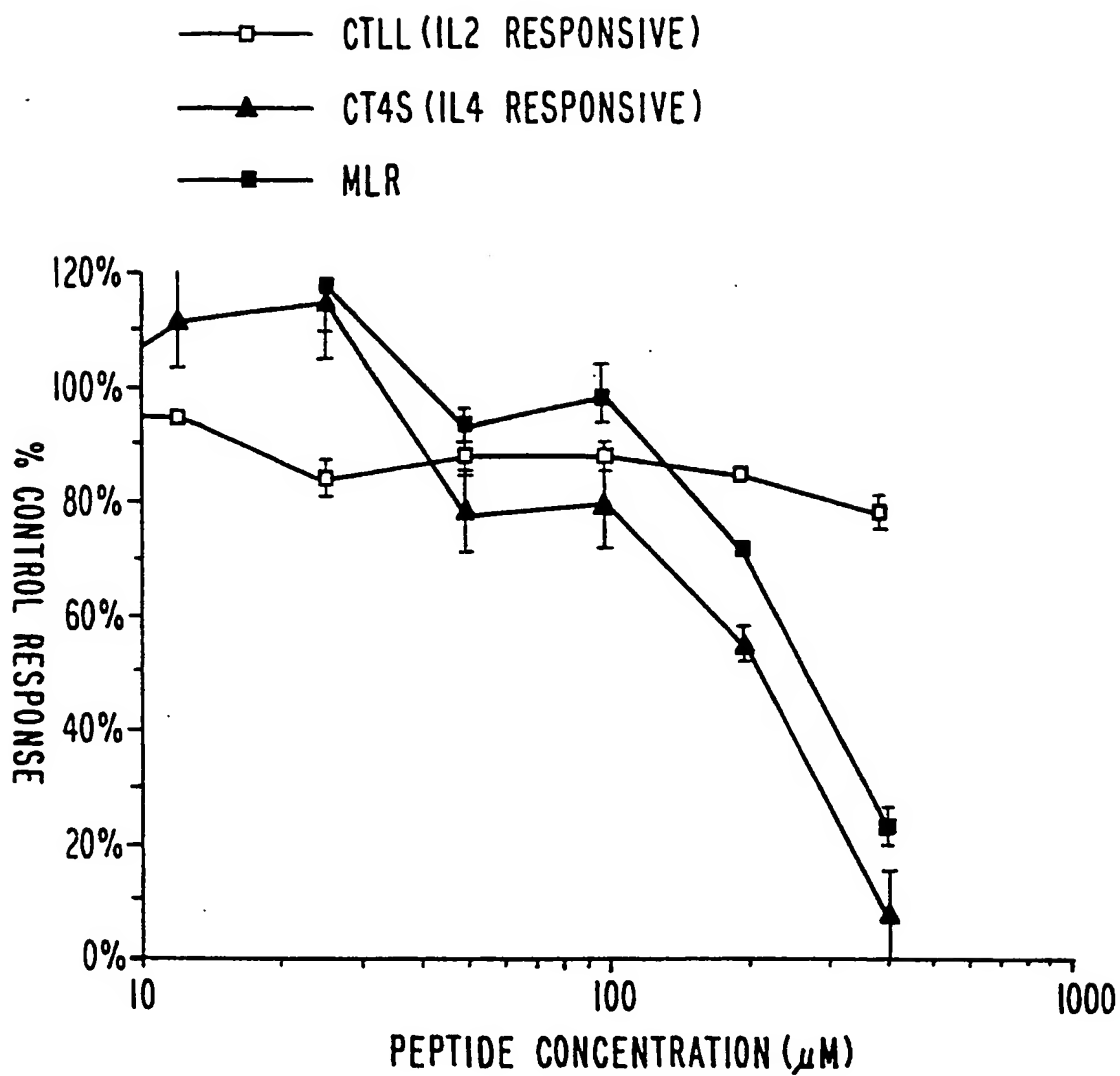
**Fig. 6F**

Fig. 7

Effect of Gamma Chain peptides on CH12 Challenge In Vivo
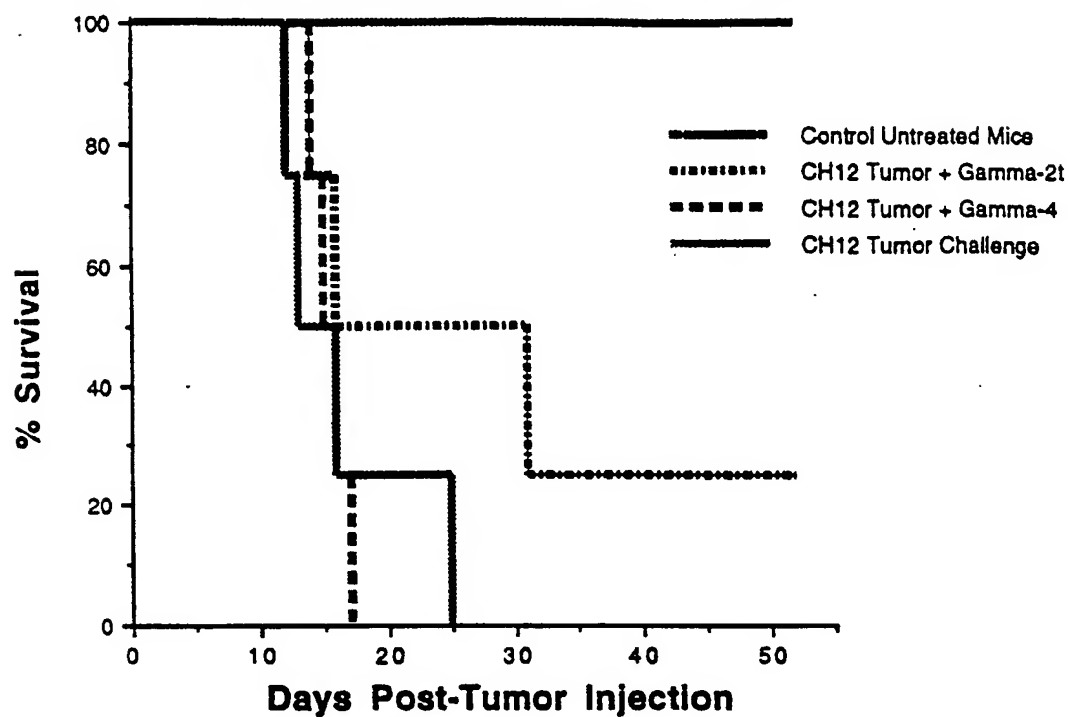
FIGURE 8

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 38/00, 38/08, 38/12
US CL : 530/317, 328, 329
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/317, 328, 329

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/11312 A1 (WASHINGTON UNIVERSITY) 27 April 1995, entire document	1-26
A,P	WO 97/28190 A1 (MEDVET SCIENCE PTY, LTD.) 07 August 1997, entire document.	1-26
A	TOWNSEND et al. Peptide Mimetics of the Cytokine Receptor Common Gamma Chain. J. of Allergy and Clin. Immunol. 1997, Vol. 99. No. 1, part 1, # 67.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 MAY 1998	1 9 JUN 1998

Name and mailing address of the ISA/US	Authorized Officer
Commissioner of Patents and Trademarks	
Box PCT	MICHAEL BORIN
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Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

   Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-26 (group 1), subgroup A

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-25 drawn to peptides and their pharmaceutical compositions and claim 26, drawn to method of inhibition of signal transduction (first method of use).

Group II, claim 27, drawn to method of inhibiting cell growth.

Group III, claims 28-29, drawn to method of treating a patient.

Group IV, claims 30-31, drawn to method of preventing a condition characterized by cytokine-mediated cell growth.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features because the peptides encompassed by generic claim 1 do not share any common structure, i.e., there is no structurally distinctive portion of the structure which is shared by all of the alternatives. Further, the peptides of the claim 1 are not the contribution over the prior art because they are suggested by references teaching the structure limitation of the peptides of the claim, i.e., peptides comprising 5-25 amino acid residues. For example, the peptide MDFQVQIFSF LLISASVIMSRG, wherein the underlined sequence is the sequence of SEQ ID No:1 with one or more conservative substitutions, is described in EP 338767. Therefore, the lack of unity is present because the linking technical feature is not a "special technical feature" as defined by PCT Rule 13.2. The first method of use (claim 26) will be examined together with the product of Group I in the scope commensurate with the elected product species (see below). Methods of use of Groups II-IV will be examined, in the scope commensurate with the elected product species, if the appropriate additional examination fees are paid.

This application contains invention of Group I directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The groups of species are as follows: SEQ ID Nos: 1, 2 and 18, 19 (subgroup a); 3, 4 and 20, 21 (subgroup b); 5, 6 and 22,23(subgroup c), and so on (9 species subgroups, a-i). Under PCT Rule 13.2, the species lack the same or corresponding special technical features because they do not share any common structure, i.e., there is no structurally distinctive portion of the structure which is shared by all of the alternatives. A reference teaching, e.g., a peptide of SEQ ID 1 would not teach or suggest a peptide SEQ ID 3, and so on.

In order for more than one species to be examined, the appropriate additional examination fees must be paid.